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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

KETOROLAC TROMETAMOL—A NEW NON-OPIOID ANALGESIC

The problem of inadequate relief of postoperative pain has been recognized for many years [1] and has been the subject of considerable research. After major upper abdominal or thoracic surgery, it has been reported that more than 50% of patients suffer severe pain [2] because of practitioners' fear that opioids may result in respiratory depression. The standard method of providing postoperative analgesia has been intermittent on-demand administration of i.m. injections of opioids, but there may be delays in administration because of the requirement for two nurses to check controlled drugs. Pressure of work on medical and nursing staff may cause inadequate assessment of pain or there may be a reluctance to administer drugs in sufficient doses because of fear of associated side effects [3]. In addition, the requirements for morphine in the first 24 h after upper abdominal surgery can vary more than 30-fold between patients who have undergone similar surgery [4].

Continuous infusion of opioids either i.v. or extradurally may lead to improved quality of analgesia, but may be associated with increased depression of respiration [5, 6]. In view of the adverse effects of opioid analgesia, there has been renewed interest in the use of non-opioid analgesics with the aim of reducing opioid requirement and thus decreasing the frequency of unwanted side effects [7–9].

Ketorolac trometamol is a new non-steroidal anti-inflammatory drug (NSAID) which exhibits potent analgesic, but only moderate anti-inflammatory activity. It has been investigated extensively for use in postoperative analgesia both as the sole agent and to supplement opioid analgesics. After i.m. injection, maximum plasma concentrations are achieved within 45–60 min [10, 11]. The drug is highly bound to plasma proteins and has a low clearance compared with opioids [10]. Ketorolac is metabolized principally by glucuronic acid conjugation, although a small amount also undergoes parahydroxylation to p-hydroxyketorolac, which has little analgesic or anti-inflammatory activity [11]. Clearance is significantly less in patients aged 65 yr or more compared with younger patients, and older patients require a lower rate of administration of ketorolac.

In a single-dose study of 149 patients who had undergone dental surgery and experienced pain of moderate to severe intensity, Brown and colleagues [12] reported better quality of pain relief from ketorolac 30 mg and 10 mg compared with pethidine 100 mg and 50 mg; in addition, the patients who received pethidine had an increased frequency of nausea and vomiting compared with those who received ketorolac. This may have been caused by early ambulation of patients and could have influenced the pain scores in favour of ketorolac. The same group also found similar benefits comparing single doses of ketorolac 30 and 10 mg with morphine 12 and 6 mg in 241 patients who had undergone major surgery and required analgesia within 48 h following surgery [13]. Again, the frequency of nausea and vomiting was greater in those receiving morphine, but not significantly so.

Studies of multiple dosing with ketorolac have confirmed its efficacy and safety when administered in doses of 10 and 30 mg after operation for up to 5 days [14–16]. A placebo-controlled study of ketorolac 30 mg 6-hourly in combination with on-demand i.m. morphine for pain after orthopaedic surgery showed that the quality of pain relief was better in the ketorolac group, but there was no difference between the two groups in consumption of morphine [unpublished observations].

When severe pain is experienced after major surgery, ketorolac may not provide adequate analgesia without opioid supplementation. Gillies and colleagues undertook a placebo-controlled, double-blind study of 57 patients who had undergone upper abdominal surgery [17]. All patients had access to morphine supplied as an i.v. bolus dose from a patient-controlled analgesia system. Patients who received ketorolac required approximately 30% less morphine compared with those who received placebo and, in addition, had lower pain scores. A study in similar patients by the same group confirmed this morphine sparing effect [18] and also reported that the continuous i.m. administration of ketorolac was more effective than intermittent administration of the same overall dose.

Adverse effects

The major benefit of ketorolac is lack of depression of the cardiovascular and respiratory systems [19, 20]. However, in common with other NSAID, there are several recognized possible adverse effects.

Haematological effects

All NSAID inhibit platelet aggregation by the reversible block of prostaglandin synthetase. Diclofenac has been shown to have no significant effect on blood loss after transurethral prostatectomy [21], but there was increased perioperative blood loss when indomethacin was used before and after hysterectomy [22]. Ketorolac produces an increase in bleeding time, but this appears to have little clinical significance in patients with normal haemostatic function, as almost all values in a study reported by Spowart and colleagues remained within the normal range [23]. This study also showed no interaction between ketorolac and the administration of low dose heparin. No controlled studies have reported increased blood loss following the use of ketorolac for postoperative analgesia.

Gastrointestinal effects

Gastric irritation is a frequent adverse effect of NSAID, but ketorolac appears to have little effect in the doses studied. The overall frequency of bleeding peptic ulceration following administration of the recommended doses of up to 120 mg day^{-1} was 0.3% in 6400 subjects [data on file, Syntex]. However, most of these occurred between 38 and 248 days during long term oral studies and a reduced frequency of occurrence may be expected when ketorolac is used for a shorter period to provide postoperative analgesia.

Renal effects

All NSAID can cause renal insufficiency by reduction in the synthesis of renal prostaglandins. When ketorolac was administered for 5 days to a group of elderly patients with impaired renal function, serum creatinine increased slightly, but returned to the previous value after administration of the drug was discontinued [data on file, Syntex]. A further study was undertaken to assess the renal effects in 67 patients who had undergone upper abdominal surgery and received ketorolac or placebo for the first 48 h after surgery [unpublished observations]. The only significant effect was a reduction in excretion of potassium in patients who received ketorolac. Ketorolac would appear, therefore, to have little potential for renal toxicity when adequate fluid balance is maintained and renal function is not dependent on renal prostaglandins. However, patients with congestive cardiac failure, hypovolaemia, or hepatic cirrhosis release vasoactive substances and, in these circumstances, prostaglandins are important to maintain renal blood flow [24]. Inhibition of prostaglandin synthesis by any NSAID may result in renal arteriolar constriction in these patients, with subsequent impairment of renal function.

Ketorolac may therefore provide adequate analgesia when used as the sole agent for most patients suffering pain of moderate intensity. Where pain is severe, some patients may require no supplementation for adequate control of pain but most may require administration of additional opioids. However, the quality of analgesia achieved may be better when ketorolac is administered regularly in addition to an opioid, with the probability of decreased frequency of adverse effects such as depression of respiration.

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COMPARISON OF I.M. KETOROLAC TROMETAMOL AND MORPHINE SULPHATE FOR PAIN RELIEF AFTER CHOLECYSTECTOMY

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SUMMARY

I.m. ketorolac trometamol 30 mg was compared with morphine sulphate 10 mg after cholecystectomy in a double-blind, multiple dose, randomized study of 100 patients. Assessments of pain were made immediately after operation (day 1), and the next morning (day 2). Pain intensity (verbal response score and visual analogue scale) was recorded before injection and then over a 6-h period. Pain relief was assessed also. The effect of ketorolac on operative blood loss and platelet function was examined. Time to commencing oral intake and the duration of administration of i.v. fluids were recorded. Adverse events were noted. Ketorolac produced significantly less analgesia than morphine on day 1, but on day 2 the two drugs produced a similar effect. Blood loss was not increased by ketorolac, although platelet function was impaired. Repeated i.m. administration of ketorolac did not produce any serious adverse effects.

KEY WORDS

Analgesics: ketorolac, morphine. Pain: postoperative

Ketorolac trometamol [1], a parenteral nonsteroidal anti-inflammatory drug (NSAID), is currently being assessed as a postoperative analgesic [2]. In animal models, ketorolac has analgesic, antipyretic, and anti-inflammatory actions attributed to prevention of prostaglandin synthesis by inhibition of the enzyme cyclo-oxygenase [3], a mechanism of action common to all aspirin-like drugs [4].

Ketorolac has compared favourably with opioids in studies of postoperative pain, and with other analgesics after minor surgery [5, 6]; 30 mg was as effective as morphine 12 mg in relieving moderate to severe pain after major surgery [7, 8]. Infusions of ketorolac reduced morphine requirement after upper abdominal surgery [9].

Ketorolac is a non-opioid analgesic and does not produce respiratory depression [10], reduction of gastrointestinal motility [11], addiction [12], or psychomotor effects [13], but NSAID have potential problems related to their mechanism of action. Prostaglandins have many physiological roles [14], and NSAID may produce side effects including gastric and duodenal ulceration, bronchospasm and renal impairment. Also, platelet cyclo-oxygenase is essential for production of thromboxane A_2 which is an important mediator of aggregation and vasoconstriction—processes which constitute the primary haemostatic response to vessel injury. Other NSAID have been reported to increase surgical blood loss [15]. Ketorolac is known to inhibit platelet function in volunteers [16, 17], but there is little information about its effect on surgical bleeding.

This study was designed to examine the efficacy and safety of multiple doses of i.m. ketorolac 30 mg compared with morphine 10 mg after cholecystectomy. The effect of ketorolac on operative blood loss, skin bleeding time and whole blood platelet aggregation was also observed.

PATIENTS AND METHODS

One hundred male and female patients undergoing elective cholecystectomy were studied. The investigation was approved by the local Ethics

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This article is accompanied by an Editorial.

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Committee and each subject gave written informed consent. Exclusion criteria were a history of ulcer disease, bleeding tendency, asthma, allergy, intolerance to aspirin, age less than 18 yr, recent administration of analgesia and abuse of drugs, alcohol or opioids.

Anaesthesia

Premedication was oral temazepam. Anaesthesia was induced with i.v. thiopentone and maintained with halothane, enflurane or isoflurane in an oxygen–nitrous oxide mixture. The trachea was intubated after administration of suxamethonium. The lungs were ventilated artificially and vecuronium or atracurium given to achieve neuromuscular block; neostigmine with atropine was given to antagonize residual block. No analgesics were used other than study medication. Subcutaneous heparin 5000 iu at the time of premedication was given to all patients as prophylaxis against venous thrombosis.

Study design

A double-blind parallel dose comparison was made of two treatment groups: ketorolac 30 mg ($n = 50$) and morphine 10 mg ($n = 50$). Patients were allocated randomly to receive ketorolac or morphine in groups of 10. The two analgesics were supplied in identical 1-ml, amber coloured ampoules in boxes of eight, numbered 1 to 100. Each patient was allocated a study number, and received all eight doses from that box.

Administration of analgesia

The first dose was given into the vastus lateralis muscle at induction of anaesthesia. Doses were then given on patient demand, up to 2-hourly, with a maximum of six doses in 24 h. Each patient was permitted to receive eight doses of study medication during the study, which lasted up to 48 h. If analgesia was inadequate, rescue medication (morphine) was given at the discretion of the nurse, and the patient continued in the study.

Efficacy

Assessments were made on the second dose of study medication (immediately after surgery, day 1) and on a dose on the morning of the next day (day 2). The patient and an independent nurse observer scored pain intensity separately before injection, and pain intensity and pain relief at 0.5, 1, 2, 3, 4, 5 and 6 h. If the patient required further analgesia or fell asleep in the 6-h study period, the last score recorded was used for the remaining observation times.

Pain scores

Scores were made by the same nurse observer. The patients gave assessments by verbal response scores and visual analogue scales.

Pain intensity scores. Pain intensity was scored by the nurse and the patient on a four-point scale (0 = no pain; 1 = mild; 2 = moderate; 3 = severe). The patient also completed 10-cm visual analogue scales (0 = no pain, to 10 cm = worst possible pain).

Pain relief scores. The observer and the patient scored pain relief on a four-point scale (0 = no relief; 1 = slight; 2 = moderate; 3 = complete), and the patient completed visual analogue scales (0 = no relief, to 10 cm = complete relief).

Derived scores. Pain intensity differences (PID) were calculated by subtracting the scores from the baseline score. The seven PID from the 6-h observation periods were added together to give summed pain intensity differences (SPID). SPID were derived for the observer and patient for days 1 and 2. The visual analogue equivalent of SPID from the patient was calculated (visual analogue SPID). Total pain relief scores (PRtot) and the visual analogue equivalent (visual analogue PRtot) were calculated by adding the scores from each observation time.

Intervals between injections. We recorded the time in minutes between the second dose (immediately after surgery) and the next analgesic injection, as a further measure of efficacy.

Morning assessments. On the morning after surgery (day 2) and the next morning (day 3) the patient was asked if s/he had slept well, if pain control was satisfactory, and about any unpleasant dreams. Oral temperature was noted.

Final assessment. At the end of the study, both patient and observer independently gave an overall opinion of analgesia as very good/good/fair/poor.

Oral intake and i.v. fluids

The time in hours was recorded from the end of surgery to established oral intake and to removal of the i.v. infusion.

Completion rates and early withdrawal

Each subject completed the study if all eight doses of medication over days 1 and 2 were received. Completion rates were compared between the groups, and reasons for withdrawal noted.

Injection site discomfort

Some NSAID produce pain and muscle damage when injected [13]. To assess if ketorolac produced this side effect the nurse noted any abnormality at the injection site. The subject rated pain on injection as none/minimal/moderate/severe.

Adverse events. All were recorded, and venous blood was sampled for haematological and biochemical analysis before and after the study period.

Haemostasis and blood loss

In all subjects, operative blood loss was estimated by weighing swabs. Within the randomization schedule in 10 subjects from each group, skin bleeding time was recorded before surgery and 1 h after the first dose of study medication. In 10 of these 20 subjects, platelet function tests were performed also at the same time. None of these 20 subjects was a cigarette smoker.

Skin bleeding times were recorded in duplicate on the forearm by the modified method of Ivy [18, 19] using a Simplate II bleeding time device to standardize the length and depth of incision. Bleeding time was taken for the two incisions and the mean time recorded. The upper limit of normal using this technique is 10 min [19].

In five subjects in each group, platelet aggregation was studied *in vitro* using a Clay-Adams Ultra-Flo whole blood platelet counter [20, 21]. Spontaneous, collagen 2 µg ml^{-1}-induced (Semmelweiss), and arachidonic acid 0.5 mmol $litre^{-1}$-induced (Sigma) aggregation were observed. Whole venous blood was anticoagulated with 3.8 % trisodium citrate. From each sample, a red cell count was first determined and dialled into the whole blood platelet counter. A 10-µl aliquot was withdrawn and the baseline platelet count determined (100 %). The aggregating agent, if used, was added and the sample stirred at a constant 1000 r.p.m. and 37 °C. Further aliquots were taken at 5 and 10 min for spontaneous aggregation, and at 1, 3 and 5 min for collagen- and arachidonic acid-induced aggregation. The platelet count at each sample time was determined as a percentage of the baseline count. Collagen- and arachidonic acid-induced aggregation depend to a large extent on thromboxane production, but spontaneous aggregation does not.

Statistical analysis

In comparing the two analgesics, the most important measurement of efficacy was SPID. As the pain scores were on an ordered four-point scale, PID at each assessment could be −3 to 3. SPID over 6 h (seven assessments) could range from −21 to 21, with a mean of zero and SD of approximately 7. Taking a significance level α of 5 %, a difference between the analgesics in SPID of 4 (approximately 10 %) could be detected with a power of 80% if the total sample size was 100 patients.

For demographic data mean (SEM) is given, and between group comparisons made using an unpaired *t* test. For other data median and range are given, and non-parametric statistical tests used. Categorical data were analysed using Fisher's exact or Pearson's chi-square test. Ordinal and interval data were analysed using the Mann–Whitney *U* test for unpaired and the Wilcoxon signed rank test for paired data. $P \leqslant 0.05$ was considered significant.

RESULTS

The groups were similar with respect to sex, age, height, weight, position of incision and duration of surgery (table I).

Efficacy (table II)

Baseline pain intensity. Pain intensity was similar for the two groups on days 1 and 2. The patients scored pain as severe on day 1 and moderate on day 2.

Pain intensity scores. Observer and patient SPID were significantly less for ketorolac than for morphine on day 1. On day 2 ketorolac and morphine gave similar results.

TABLE I. *Patient details. Type of abdominal incision and duration of operation. Mean (SEM) where appropriate*

	Ketorolac	Morphine
Sex (M/F)	17/33	13/37
Age (yr)	53.5 (2)	52.3 (2.1)
Height (cm)	166.2 (1.4)	164.0 (1.1)
Weight (kg)	69.4 (1.7)	67.3 (1.8)
Subcostal	39	37
Midline	11	13
Duration (min)	86 (3.9)	91 (5.1)

TABLE II. *Baseline pain score, SPID and PRtot over 6 h, by nurse observer and the patient. Median (range).* n = *Number of patients observed at each time*

	Ketorolac	Morphine	*P*
Baseline			
Observer			
Day 1	2 (1–3)	2 (2–3)	0.48
Day 2	2 (1–3)	2 (1–3)	0.18
Patient			
Day 1	3 (2–3)	3 (2–3)	0.99
Day 2	2 (1–3)	2 (1–3)	0 2
Patient visual analogue			
Day 1	8.05 (5.2–10)	8.0 (6.3–10)	0.42
Day 2	5.15 (1–10)	6.35 (0.9–9.9)	0 13
SPID			
Observer			
Day 1	0 (−7 to 12)	7 (0–14)	0.0001
n	48	45	
Day 2	7 (0–10)	6 (−5 to 13)	0.9
n	36	38	
Patient			
Day 1	0 (−7 to 11)	6 (0–13)	0 003
n	32	30	
Day 2	1 (−5 to 13)	5 (−11 to 13)	0.21
n	37	38	
Patient visual analogue			
Day 1	0.7 (−8.1 to 42.7)	10.85 (−11.2 to 42)	0.11
n	19	18	
Day 2	11.2 (−13.6 to 47)	13.2 (−33.9 to 52 2)	0.41
n	37	37	
PRtot			
Observer			
Day 1	1.5 (0–14)	13 (0–20)	0.0001
n	48	45	
Day 2	13.5 (0–21)	12.5 (2–20)	0.79
n	36	38	
Patient			
Day 1	0 (0–14)	6 (0–20)	0.029
n	34	30	
Day 2	12 (0–21)	12 (2–16)	0.62
n	37	38	
Patient visual analogue			
Day 1	4.6 (0–53.2)	8.6 (0–45.8)	0 24
n	19	19	
Day 2	32 (0–70)	37.25 (5.8–63)	0.61
n	37	38	

Visual analogue SPID was less for ketorolac on day 1, but the difference was not statistically significant. On day 2 there was no difference.

Pain relief scores. Observer and patient PRtot were significantly less for ketorolac on day 1, but on day 2 there was no difference.

Visual analogue PRtot showed no difference between the drugs on each day.

Intervals between injections and rescue morphine (table III). After the second dose of study medication, patients receiving ketorolac required repeat analgesia sooner than those receiving morphine. In the first 24 h of the study the ketorolac group required more rescue medication than the morphine group. In the second 24 h there was no difference between the groups.

Morning assessments (table IV). The patients in the two groups reported similar satisfaction with overnight sleep and pain relief. There was no difference in the incidence of psychological disturbances or pyrexia.

Final assessment (table V). There was no statistical difference between the overall opinions of the patients or observers of the study medi-

TABLE III. *Time from second dose to next injection and daily requirements for rescue morphine. Median (range)*

	Ketorolac	Morphine	*P*
Time (min)	72.5 (15–1125)	207.5 (20–915)	0.0001
Morphine (mg)			
Day 1	10 (0–36)	0 (0–55)	0.003
Day 2	0 (0–10)	0 (0–10)	0.9

TABLE IV. *Morning assessments*

	Ketorolac	Morphine	*P*
Day 2			
Satisfactory sleep? (Yes/No)	26/20	25/22	0.74
Satisfactory analgesia? (Yes/No)	36/10	38/9	0.76
Psychological disturbances? (Yes/No)	8/38	8/39	0.96
Temperature > 38 °C? (Yes/No)	2/44	4/43	0.41
Day 3			
Satisfactory sleep? (Yes/No)	19/7	26/7	0.61
Satisfactory analgesia? (Yes/No)	24/2	32/1	0.42
Psychological disturbances? (Yes/No)	2/24	2/31	0.80
Temperature > 38 °C? (Yes/No)	0/26	2/31	0.20

TABLE V. *Overall opinion of study medication, time to oral intake and duration of i.v. infusion, completion rates, injection site abnormality and pain. Median (range)*

	Ketorolac	Morphine	*P*
Patient			
Very good	21	23	0.22
Good	17	16	
Fair	3	4	
Poor	6	0	
Observer			
Very good	22	21	0.91
Good	13	13	
Fair	7	8	
Poor	6	4	
Oral intake (h)	27.5 (18–50)	30 (20–112)	0.16
Infusion (h)	48.5 (25–108)	51.5 (26–200)	0.047
Completion rate			
Completed	19	27	0.16
Withdrew	31	23	
Injection site abnormality (Yes/No)	10/39	7/41	0.59
Pain on injection			
None	35	36	0.65
Minimal	11	7	
Moderate	3	4	
Severe	0	0	

cation. Nevertheless, six patients who received ketorolac described their analgesia as poor.

Oral intake and i.v. fluids (table V). The time until oral intake recommenced was not different between the groups, but the morphine group received i.v. fluids for longer.

Completion rates and early withdrawal (table V). The completion rate was similar for the two groups, but more patients withdrew in the ketorolac group. The most common reason for early withdrawal was that parenteral analgesia was no longer required and oral therapy was started. Failure of analgesia accounted for seven and two withdrawals from the ketorolac and morphine groups, respectively.

Injection site abnormalities and pain (table V). There was no difference in the incidence of injection site abnormality or pain on injection between the groups.

Adverse events. Ketorolac produced more nausea ($P = 0.005$) and vomiting ($P = 0.05$) on the day of operation, but not on the day after ($P = 0.73$, and 0.85, respectively). Morphine was associated with a greater incidence of drowsiness on days 1 ($P = 0.0001$) and 2 ($P = 0.007$).

Two patients from the ketorolac group and four from the morphine group were withdrawn because of severe adverse events. In the ketorolac group, one patient was returned to theatre because of continuing blood loss; an obvious source was controlled. Another of the ketorolac group developed a chest infection. Two of the morphine group had excessive postoperative blood loss. One was returned to theatre, but no obvious bleeding vessel was found; the other required a blood transfusion only. Two of the morphine group developed chest infections; one also experienced severe drowsiness which was treated with naloxone. No other serious adverse events were reported. No abnormal changes were detected on biochemical or haematological analysis of blood.

Haemostasis and blood loss (table VI)

Operative blood loss. There was no statistical difference in the blood loss of the two groups ($P = 0.5$); the median loss of the ketorolac group was 192 ml (range 20–580 ml), and the morphine group 162 ml (25–950 ml).

TABLE VI. *Bleeding time and platelet aggregation before and 1 h after the first i.m. injection. Whole blood platelet aggregation is expressed by the percentage of platelets present in the sample at each time (baseline count = 100%). Median (range)*

	Before	After	*P*
Skin bleeding time (s)			
Ketorolac	222 (155–340)	299 (215–369)	0.01
Morphine	244 (177–308)	246 (175–299)	0.51
Platelet aggregation			
Spontaneous			
5 min:			
Ketorolac	63 (43–66)	62 (45–75)	0.13
Morphine	56 (41–68)	50 (41–75)	0.86
10 min:			
Ketorolac	49 (26–58)	44 (38–58)	0.81
Morphine	43 (31–50)	46 (32–58)	0.42
Collagen			
1 min:			
Ketorolac	23 (11–48)	47 (21–100)	0.28
Morphine	13 (6–33)	14 (7–24)	0.79
3 min:			
Ketorolac	15 (9–18)	49 (13–84)	0.06
Morphine	8 (5–19)	7 (5–14)	0.42
5 min:			
Ketorolac	16 (10–19)	27 (16–79)	0.06
Morphine	9 (8–20)	10 (5–14)	0.89
Arachidonic acid			
1 min:			
Ketorolac	33 (8–91)	57 (29–84)	0.42
Morphine	11 (8–68)	10 (6–30)	0.11
3 min:			
Ketorolac	21 (7–56)	53 (24–61)	0.18
Morphine	11 (7–42)	9 (6–14)	0.59
5 min:			
Ketorolac	23 (11–41)	55 (24–61)	0 18
Morphine	10 (8–19)	9 (8–16)	0.20

Skin bleeding time. This was prolonged significantly by ketorolac from a median of 222 s to 299 s. After ketorolac, the longest bleeding time was 369 s—an increase of 214 compared with control, but within the normal upper limit of 600 s. The morphine group showed no change in bleeding time.

Platelet aggregation. Spontaneous platelet aggregation was unchanged after ketorolac. Collagen- and arachidonic acid-induced aggregation tended to be reduced by ketorolac, but statistical significance was approached only for collagen-induced aggregation at 3 and 5 min. There was no change in the morphine group.

DISCUSSION

After cholecystectomy, ketorolac 30 mg gave poor analgesia in the immediate postoperative period when compared with morphine 10 mg, but on the next day the effect of the two drugs was similar. This was demonstrated by observations of pain intensity, pain relief, time to next injection, and overall assessment of analgesia. The baseline pain intensity in the immediate postoperative period was severe, and the next day it was moderate. Our findings suggest that an i.m. dose of ketorolac 30 mg is sufficient for the relief of moderate, but not severe pain.

Other observers found that ketorolac 30 mg was at least as effective as morphine 12 mg in relieving moderate to severe pain after various operations, including major surgery [7, 8]. As these were single-dose studies performed up to 2 days after surgery, they should be compared with our day 2 results, to which they are similar.

Our conclusion that ketorolac is unsuitable for the relief of severe pain is similar to that from studies on the analgesic effect of a parenteral formulation of aspirin. Lysine acetyl salicylate is a poor analgesic compared with morphine as a bolus in the immediate postoperative period [22], but equivalent to morphine when given as an infusion over a period of time [23].

Although ketorolac was a poor analgesic in the immediate postoperative period, the ketorolac group expressed overall satisfaction with their analgesia, and required only a small dose of rescue morphine (10 mg) in the first 24 h and none the next day. Such results may indicate that the quality of ketorolac analgesia became similar to that of morphine after the initial postoperative period. A morphine sparing effect of ketorolac after abdominal surgery has been documented before [9].

Ketorolac does not inhibit gut motility [11], and in this study the patients receiving ketorolac required i.v. fluids for a shorter time, although the time to oral intake did not differ between groups. This may be important because ketorolac will also be available as tablets which could be used when the patient is able to take fluids. It was noted that many patients in this study required parenteral analgesia for only a short time after cholecystectomy.

I.m. ketorolac did not produce more injection site pain or abnormalities than morphine. Ketorolac given as repeated i.m. injections does not increase serum concentrations of creatine phosphokinase, but diclofenac does [13]. The muscular discomfort produced by injections of diclofenac may not be a problem with ketorolac.

With the exception of six patients, adverse events were minor. Ketorolac was associated with more nausea and vomiting on the day of operation, and drowsiness and sedation were persistent problems with morphine, as could be predicted from studies on psychomotor effects of ketorolac and opioids [13]. No serious side effects resulted from repeated administration of ketorolac over 2 days. In particular, there were no untoward gastrointestinal or renal effects. As the adverse renal effects of NSAID are serious and well documented [24], more detailed studies of the effect of ketorolac on kidney function are required before the intraoperative use of the drug can be recommended.

Ketorolac 30 mg did not increase operative blood loss, although it prolonged skin bleeding time and tended to inhibit platelet aggregation, as observed in volunteer studies [16, 17]. The effect was similar to that of a single dose of aspirin and may be clinically insignificant because none of the bleeding times was abnormal after ketorolac [25]. Nevertheless the effect of NSAID on operative blood loss is still unclear. Blood loss is increased by indomethacin after hysterectomy [15], but not by diclofenac after gynaecological laparotomy [26] or transurethral prostatectomy [27]. As indomethacin, diclofenac and ketorolac have the same mechanism of action, a similar effect on blood loss could have been expected. The surgical procedure and the dose of NSAID could be important, and some patients may react excessively if they have a subclinical haemostatic defect [28].

Ketorolac is therefore a clinically useful parenteral analgesic after upper abdominal surgery and 30 mg i.m. is adequate for relief of pain of moderate intensity.

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EFFECTS OF RANITIDINE AND METOCLOPRAMIDE ON GASTRIC FLUID pH AND VOLUME IN CHILDREN†

S. CHRISTENSEN, A. FARROW-GILLESPIE AND J. LERMAN

SUMMARY

To determine the effects of ranitidine and metoclopramide on gastric fluid in children, 40 healthy children (aged 2–8 yr) were allocated randomly to groups of 10 to receive one of four oral premedications 4 h before surgery: no premedication, metoclopramide 0.1 mg kg^{-1}, ranitidine 2 mg kg^{-1} and metoclopramide 0.1 mg kg^{-1} with ranitidine 2 mg kg^{-1}. After tracheal intubation, gastric fluid was aspirated and analysed for pH and total fluid volume. Ranitidine, with or without metoclopramide, increased gastric fluid pH significantly compared with control ($P < 0.05$). Gastric fluid volume did not change significantly.

KEY WORDS

Anaesthesia: paediatric. Gastrointestinal tract: gastric fluid volume, gastric pH. Premedication: metoclopramide, ranitidine.

The severity of lung damage following gastric fluid aspiration is determined often by the pH and volume of the fluid aspirated [1, 2]. Evidence from animal studies indicates that the lung damage is most severe when the pH of the aspirated fluid is < 2.5 and volume > 0.4 ml kg^{-1} [3]. If these criteria hold true for humans also, then those patients with a gastric fluid pH < 2.5 and volume > 0.4 ml kg^{-1} are at risk of severe lung damage following gastric fluid aspiration. Several studies have shown that 75% of healthy children who fast before elective surgery have a gastric fluid pH < 2.5 and volume > 0.4 ml kg^{-1} [4, 5]. In these children, aspiration of gastric fluid may cause severe lung damage.

Recent efforts to minimize the severity of lung damage following aspiration of gastric fluid have focused on two groups of drugs: histamine type 2 (H_2) receptor antagonists [6, 7] and benzamide derivatives [8–10]. Ranitidine, one of the newer H_2 receptor antagonists, reduces the risk of lung damage by decreasing gastric acid secretion without affecting lower oesophageal sphincter tone or gastrointestinal motility. In a dose of 2 mg kg^{-1}, it increases gastric fluid pH and decreases gastric fluid volume without affecting gastric emptying [6, 7, 11]. In contrast, metoclopramide, a benzamide derivative, reduces the risk of lung damage by increasing lower oesophageal sphincter tone, enhancing gastric emptying and augmenting intestinal motility without altering gastric acid secretion [8–10]. Although metoclopramide has been shown to decrease the incidence of vomiting after chemotherapy and the severity of reflux oesophagitis in children [9, 12, 13], its effect on gastric fluid pH and volume in healthy children undergoing elective surgery is unknown. In order to compare the effects of these two drugs on gastric fluid pH and volume, we designed the following randomized, controlled and double-blinded study.

PATIENTS AND METHODS

With approval from the Human Subjects Review Committee, written informed consent was obtained from the parents of 40 children, aged 2–8 yr and ASA grade I–II undergoing elective in-patient surgery. These children were allocated randomly to groups of 10 to receive one of four oral premedications: control (no premedication), metoclopramide 0.1 mg kg^{-1}, ranitidine 2 mg

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kg^{-1}, and the combination of metoclopramide 0.1 mg kg^{-1} and ranitidine 2 mg kg^{-1}. Oral ranitidine was prepared by suspending the i.v. formulation in a fruit syrup (15 mg ml^{-1}). Oral metoclopramide was administered as a suspension (1 mg ml^{-1}). The volumes of the premedicants were 0.13 ml kg^{-1} for ranitidine and 0.1 ml kg^{-1} for metoclopramide. All children received also water 2 ml kg^{-1} approximately 4 h before surgery. No other premedicants were administered.

After administration of i.v. atropine 0.02 mg kg^{-1}, anaesthesia was induced with thiopentone 4–7 mg kg^{-1}. Tracheal intubation was facilitated with i.v. suxamethonium 2 mg kg^{-1} and anaesthesia was maintained with either halothane or isoflurane and nitrous oxide in oxygen.

After tracheal intubation but before surgical incision, an orogastric tube (Salem 16 gauge) was inserted into the stomach. The position of the orogastric tube was verified by injecting air into the tube and auscultating over the epigastrium. The pH of a 2-ml sample of gastric fluid aspirate was determined using a pHM62 Radiometer pH meter. The pH meter was calibrated using three standard pH solutions: 1.0, 4.01 and 7 before each measurement. Several attempts were made to remove all the gastric fluid by blind aspiration. To facilitate this, pressure was applied over the epigastrium with the patient in the left lateral decubitus position while gentle suction was applied manually to the orogastric tube. Gastric fluid volume was defined as the total volume of fluid aspirated. Gastric fluid pH and volumes were determined by one of the authors who was blinded to the patient's premedication.

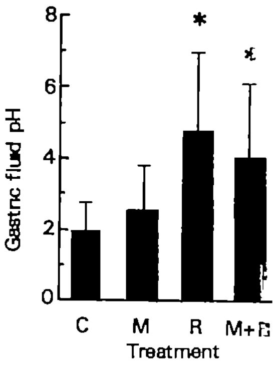

FIG. 1. Mean (SD) gastric fluid pH. *Significantly greater in the ranitidine groups with or without metoclopramide compared with control ($P < 0.05$).

The patient's age, weight, fasting interval and pH and volume of the gastric fluid aspirate were recorded.

The frequency distributions of gastric fluid pH and volume for each group were tested for deviation from normality with the Kolmogorov–Smirnov test. Statistical significance ($P < 0.05$) was determined using one-way analysis of variance and the Tukey test [14] for multiple pairwise comparisons for age, weight, fasting interval, and gastric fluid pH and volume. Power analysis was applied to negative results using standard techniques [15]. All data are presented as means (SD).

RESULTS

The ages, weights and fasting intervals of the four groups did not differ significantly (table I). Gastric fluid was obtained from all 40 patients.

Gastric fluid pH in the control group did not

TABLE I. *Details of patients studied (mean (SD)). § Time interval from last fluids and premedication until gastric fluid sampling.* $P < 0.05$: **compared with control; † compared with metoclopramide*

	Treatment group			
	Control	Metoclopramide 0.1 mg kg^{-1}	Ranitidine 2 mg kg^{-1}	Metoclopramide 0.1 mg kg^{-1} and ranitidine 2 mg kg^{-1}
Number of patients	10	10	10	10
Age (yr)	4.41 (2.39)	5.63 (1.75)	4.62 (1.58)	5.65 (2.17)
Weight (kg)	18.9 (8.5)	21.5 (6.6)	17.2 (3.5)	21.8 (9.8)
Fasting interval (h)§	5.23 (1.64)	4.26 (0.95)	4.14 (0.41)	4.29 (0.63)
Gastric fluid				
pH	1.90 (0.87)	2.41 (1.4)	4.76 (2.2)*†	4.07 (2.0)*
Volume (ml kg^{-1})	0.43 (0.11)	0.49 (0.33)	0.47 (0.29)	0.40 (0.19)
Children with pH < 2.5 and volume > 0.4 ml kg^{-1} (%)	50	40	10	20

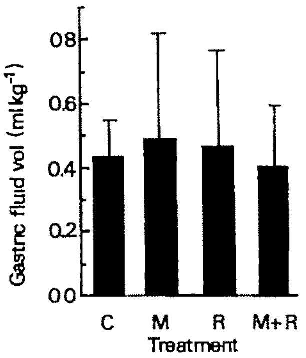

FIG. 2. Mean (SD) gastric fluid volume. No significant difference in the ranitidine, metoclopramide and combination groups compared with control.

differ significantly from that in the metoclopramide group (table I, fig. 1). However, gastric fluid pH was significantly greater in both the ranitidine and ranitidine–metoclopramide groups compared with the control group ($P < 0.05$). Gastric fluid pH in the ranitidine group did not differ statistically from that in the ranitidine–metoclopramide group.

There was no difference between the groups with regard to gastric fluid volume (table I, fig. 2).

The percentage of children with a gastric fluid pH < 2.5 and volume > 0.4 mg kg^{-1} was 50 % in the control group and 10 % in the ranitidine group. This difference was not statistically significant, but the power of this comparison was only 0.54. To achieve a power of 0.8, 18 children would be required in each group.

There were no side effects associated with the administration of ranitidine, metoclopramide or the combination of drugs.

DISCUSSION

The results of this study indicate that oral ranitidine 2 mg kg^{-1} with or without metoclopramide 0.10 mg kg^{-1} increased significantly the gastric fluid pH, but did not affect gastric fluid volume in fasted children undergoing elective surgery. The results for ranitidine are consistent with data published previously for children [6], while the results for metoclopramide support the suggestion that oral metoclopramide 0.1 mg kg^{-1} given 4 h before surgery affects neither gastric acid secretion nor gastric fluid emptying in children.

We administered oral ranitidine 2 mg kg^{-1} 4 h before surgery in an attempt to suppress gastric acid secretions completely. The dose of ranitidine was based on the results of two studies in which oral ranitidine 1.25–1.90 mg kg^{-1} suppressed gastric acid secretions effectively [16] and oral ranitidine 2 mg kg^{-1} increased gastric fluid pH and decreased gastric fluid volume in children as effectively as larger doses of ranitidine [6]. The time interval between oral ranitidine and gastric fluid measurements is an important determinant of the extent of gastric acid suppression. Blumer and others reported that the serum concentration of ranitidine was greatest, and the gastric acid secretions were least, 2 h after oral ranitidine in a group of children (mean age 12.6 (SD 3.7) yr) [16]. Although comparable data in younger children are not available, preliminary pharmacokinetic data suggest that blood concentrations of ranitidine in younger children are similar to those in older children [17]. In order to minimize gastric acid secretions in all children who received ranitidine in this study, we administered all premedicants 4 h before induction of anaesthesia.

The primary mechanism of action of metoclopramide on gastric fluid characteristics is believed to be a direct action on gastrointestinal motility. It increases lower oesophageal sphincter tone and enhances gastric fluid emptying [18]. However, two studies suggested that metoclopramide increases gastric fluid pH also. This effect was observed after a single oral dose of metoclopramide 0.15 mg kg^{-1} was given 2–2.5 h before gastric fluid aspiration [19, 20]. Although the mechanism by which metoclopramide increases gastric fluid pH is unclear, Manchikanti and colleagues suggested that metoclopramide diluted the residual acid-containing fluid in the stomach by non-acid-containing secretions [19]. Our inability to demonstrate an effect of metoclopramide on gastric fluid pH in this study may be attributed to four factors. First, the small sample size ($n = 10$) and low power (0.25) of our study. (To achieve a power of 0.80, the sample size should be increased to 65 children per group [15].) Second, an inadequate dose of metoclopramide may have been used. Third, the longer time interval between administration of the drug and aspiration of gastric fluid may have been a factor and, finally, metoclopramide may lack any direct effect on gastric fluid pH [21]. The dose of metoclopramide in this study (0.10 mg kg^{-1}) is less than that which has been reported to increase gastric fluid pH in adults (0.15 mg kg^{-1}) [19, 20]. We selected the dose of metoclopramide in consultation with the local manufacturer (AH Robins, Canada Ltd) in order to minimize the risk of side effects. These data suggest that metoclopramide alone neither decreased gastric fluid volume nor increased gastric fluid pH.

Concern has been expressed on the risks of extrapyramidal side effects after administration of metoclopramide to children. Such side effects have been reported in children who received large doses of metoclopramide (1.0 mg kg^{-1} or greater) repeatedly for nausea and emesis during chemotherapy [22, 23]. In this study, none of the 20 children who received a single oral dose of metoclopramide 0.1 mg kg^{-1} experienced any side effects. Indeed, there have been no reports of extrapyramidal side effects in healthy unpremedicated children after a single oral dose of metoclopramide. These data indicate that single dose oral metoclopramide 0.1 mg kg^{-1} may be safe for use in children [18].

Should routine premedication be administered to all fasted children who are scheduled for elective surgery? The incidence of regurgitation and gastric fluid aspiration is approximately 1:10000 [24]. Because the incidence of side effects from prophylactic therapy may exceed the incidence of pneumonitis following aspiration, there is insufficient evidence to support routine premedication at this time. Nonetheless, there is a group of children who are at increased risk of regurgitation and aspiration, including those with hiatus hernia, hyperacidity syndrome and gastro-oesophageal dysmotility. These children may benefit from prophylactic premedication to prevent aspiration pneumonitis, as we demonstrated that ranitidine reduced the percentage of children with a $pH < 2.5$ and volume > 0.4 mg kg^{-1} from 50% to 10%.

Gastric fluid volume is difficult to measure accurately in children. There are two techniques that are used commonly to estimate gastric fluid volume: the aspiration and dye dilution techniques. Although the former technique is used commonly, it may underestimate gastric fluid volume by emptying the stomach incompletely. This concern is supported by recent data in adults in whom blind aspiration yielded gastric fluid volumes that were only 50% of those obtained by direct endoscopic examination for residual fluids [25]. However, several authors have presented conflicting views on the accuracy of blind aspiration in adults [25–27]. The accuracy of blind aspiration as an estimate of the actual gastric fluid volume in children remains uncertain. The second technique available is the dye dilution technique. This technique may overestimate gastric fluid volume [28] because of incomplete mixing of dye with gastric fluid and passage of dye into the duodenum or oesophagus. We believe that both blind aspiration and dye dilution techniques may be associated with inherent errors that could be exaggerated in children who have small gastric fluid volumes.

In conclusion, we found that oral ranitidine 2 mg kg^{-1} with or without metoclopramide 0.10 mg kg^{-1} increased gastric fluid pH without affecting gastric fluid volume in healthy children scheduled for elective surgery under general anaesthesia. In view of the low risk of aspiration, we do not recommend the routine use of H_2 receptor blockers in healthy children undergoing elective surgery.

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COMPLICATIONS OF NASOTRACHEAL INTUBATION IN NEONATES, INFANTS AND CHILDREN: A REVIEW OF 4 YEARS' EXPERIENCE IN A CHILDREN'S HOSPITAL

A. E. BLACK, D. J. HATCH AND N. NAUTH-MISIR

SUMMARY

A computerized database was set up to study the incidence and outcome of complications of nasotracheal intubation in a paediatric hospital. We studied 2953 intensive care admissions over a 4-yr period. The overall complication rate was 8%. Accidental extubation and tube blockage were the most frequent events, accounting for a mean of 3.5% and 2.6% of the complications per year, respectively. Complications were more common in smaller children and there were differences between fields of intensive care. None of the complications was fatal or resulted in serious sequelae. None of the children in the study showed clinical symptoms of acquired subglottic stenosis before discharge from hospital, and none has been readmitted for this condition subsequently.

KEY WORDS

Anaesthesia: paediatric. Intubation, tracheal: complications, nasotracheal intubation.

Prolonged tracheal intubation was recommended as a useful alternative to tracheostomy more than 20 yr ago [1, 2] and, since then, has been the main method of airway support during intensive care in children.

The most important complications noted in the early reports were tube displacement, tube obstruction and post-extubation stridor [3], leaving 2–4% of patients with intractable subglottic stenosis [4–7]. Fatalities were described from each of these complications.

The advent of computerized databases has allowed comprehensive data collection, retrieval and analysis to be performed. We therefore decided to design a prospective database to allow analysis of all intubation-related complications. This paper describes the reported complications in 2953 intensive care admissions requiring periods of tracheal intubation in patients in the first 4 yr of data collection, from January 1985 to December 1988.

METHODS

A basic data sheet has been used for each intensive care patient for many years. This sheet was modified to include all complications of tracheal intubation and the reasons for reintubation when this occurred (table I). This information was transferred to a database using the Data Base II compatible software program, "Friday!" set up on a North Star Advantage computer with a 5-megabyte hard disc. Each year's results were analysed separately and then combined.

RESULTS

In the 4-yr study period, a total of 2791 intensive care patients required tracheal intubation (table II). The nasal route was used in all children aged up to the early teens, using the method of fixation described by Reid and Tunstall [8]. In children requiring intubation for more than 1 week, tubes have been changed routinely every 10–14 days, although it is recognized that many regard this as unneccessary. Forty-seven patients in 1985, 25 in

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TABLE I. *Details of respiratory data sheet and definitions*

Front

NAME
D. O. B. Hosp. No. Ward: Wt:
DIAGNOSIS:
Intubated on arrival? Y/N (indicate size & type)
Cole: Plastic Nasal: Plastic Oral: Other:
1st GOS Tube: Age: years mths days hours
Date: Time: Size: Length: Reason: Extubation Date & Time:
1 st
2 nd
3 rd
4 th

Back

Respiratory Score: 1 2 3 4 Prongs? Y/N
Complications?
Tracheostomy Y/N Reason:
Death while intubated Y/N
If weaning took longer than 72 hours please state main reason:
Stage of nostril at extubation: 1 2 3 4
Progress:

Reasons for intubation
A = Failed extubation
B = Blocked tubes
C = Accidental extubation
D = Tube too long
E = Tube too short
F = No leak
G = Excessive leak
H = Stridor on extubation
N = None
R = Routine

Respiratory score
1 = IPPV at any time
2 = Spontaneous ventilation
3 = CPAP only
4 = Prong only

Complications
B = Blocked tube
C = Accidental extubation
H = Stridor on extubation
M = Nasal ulceration
N = None
T = Bronchial intubation
V = Disconnection

TABLE II. *Number of intubations and patients*

	1985	1986	1987	1988	Total
No. of ICU admissions requiring intubation	776	625	725	827	2953
No. of patients	729	600	690	772	2791
Total no. intubations	944	842	917	831	3534

TABLE III. *Number of intubations per admission 1985–1988*

	No. intubations				
	1	2	3	4	> 5
Percent of children	80.5	14.4	2.7	1.6	0.8

TABLE IV. *Age distribution on admission 1985–1988*

Age	No.	%
< 28 days	749	25
28 days–1 yr	914	31
1–5 yr	729	25
5–10 yr	321	11
> 10 yr	240	8

TABLE V. *Duration of intubation*

	Duration of intubation (days)			
	< 2	2–7	7–14	> 14
Percent of children	51	29	11	9

1986, 35 in 1987 and 55 in 1988 had a second admission to one of the intensive care wards and required further periods of intubation, so that a total of 2953 data sheets were analysed. The majority of children (80 %) underwent intubation only once on each admission; 14.4 % underwent intubation twice and 5.1 % on more than two occasions (table III). The maximum number of intubations in any admission was eight. The ages of the patients at the time of initial intubation on each admission are shown in table IV. Ages ranged from within 4 h of birth to 19 yr, with 25 % within the neonatal period and 56 % infants younger than 1 yr. More than 80 % of patients were younger than 5 yr. Four hundred and forty-three patients died whilst receiving intensive care, an overall mortality of 15.9 %.

The duration of intubation is shown in table V and distribution of patients between the four main intensive care wards in table VI. More than 50 % of all patients underwent intubation for less than 48 h and 20 % for more than 7 days. The longest period of intubation on any admission was 90 days. Although the majority of admissions (53 %) were cardiac, the duration of intubation tended to be shorter in these children, who occupied 46 % of the total intubation days (table VII). Patients admitted to the neonatal surgical intensive care ward tended to require intubation of the trachea for longer periods than those on the other intensive care wards (12 % of admissions occupying 21 % of the intubation days).

TABLE VI. *Distribution of patients between four main intensive care areas, for years 1985–1988*

	Admissions per ward	
	Total No.	%
Cardiac	1567	53
Respiratory/medical	824	28
Neonatal surgery	340	11.5
Neurosurgery	174	6
Other	48	1.5

TABLE VII. *Intubation days per ward 1985–1988*

Ward	Percent of total intubation days
Cardiac	46.4
Respiratory/medical	27.8
Neonatal surgery	21
Neurosurgical	2.3
Other	2.5

During the period of the study 239 complications were reported, with an overall complication rate of 8 % (table VIII). None of these complications was fatal or caused cardiac arrest, and no long term sequelae were identified in any patient.

The commonest complications were accidental extubation and tube blockage, requiring immediate re-intubation in 75 % and 90 % of patients in whom they occurred, respectively. Both of these complications were more frequent in the younger patients. Eighty per cent of the accidental extubations occurred in infants aged less than 1 yr and 80 % of the blockages occurred in tubes of i.d. 3.5 mm or less. Stridor occurred after extubation in 44 subjects, but was severe enough to require a further short period of intubation in only 21 patients. In no case did it lead to the development

TABLE VIII. *Complications*

	1985	1986	1987	1988	Total	%
Accidental extubation	23	19	22	41	105	3.5
Tube blockage	13	22	23	19	77	2.6
Stridor	14	8	11	11	44	1.5
Nasal ulceration	4	0	2	3	9	0.3
Bronchial intubation	0	0	2	2	4	0.1
Total	54	49	60	76	239	
%	6.9	7.8	8.2	9.2	8.08	

TABLE IX. *Laryngeal pathology causing stridor, 1985–1988*

Diagnosis	No. patients
Haemangioma with tracheal involvement	2
Tracheomalacia	3
Congenital subglottic stenosis (Down's syndrome in one)	3
Croup	1
Tracheo-oesophageal fistula	2
Bilateral vocal cord palsy	1
Vater syndrome	1
Laryngeal tuberculosis	1
Total	14

of clinical symptoms of acquired subglottic stenosis before discharge. Pre-existing laryngeal pathology, causing stridor was present in 14 patients (table IX). Bronchial intubation was reported in four patients and nasal ulceration in nine. One hundred and eleven patients (4%) required tracheotomy during their period of intensive care.

DISCUSSION

The advantages of long term nasotracheal intubation in infants and small children as an alternative to tracheostomy have been recognized for many years [1, 2]. The main complications described in the early series were accidental extubation, tube blockage and subglottic stenosis, all of which caused fatalities [3]. Other less serious complications have been reported also [9]. In an early study from this hospital [7], the overall mortality was 3.6%. In that series, accidental extubation occurred in three of 167 intubations (one death) and tube obstruction occurred in eight (four deaths). Subglottic stenosis occurred in three cases (one death).

The complication rate in the present study was 8%, varying between 6.9% and 9.2% annually during the study. In contrast with the earlier series, no complication resulted in death or other serious sequelae.

Accidental extubation and tube obstruction remained the commonest complications. It is difficult to compare the incidence of accidental extubation or tube blockage in this series with that reported from this hospital in 1968 [7], as the incidence related to days of intubation was not reported in the earlier paper. However, both these complications still occur regularly. Although accidental extubation is less likely to occur when neuromuscular blocking drugs are used, the risk of hypoxic sequelae is increased. The absence of mortality or serious morbidity from each complication in this series probably results from the infrequent use of neuromuscular blocking drugs and improvements in patient monitoring. There have been no cases of clinically significant subglottic stenosis produced within the hospital since the policy was adopted of ensuring that a slight leak occurs around the tube with the application of 25 cm of pressure to the airway [10], although stridor did occur after extubation in 1.5% of patients.

Accidental extubation

While individual tube lengths should be determined at intubation by direct vision, and confirmed by x-ray, a formula based on actual tube lengths recorded in this study (internal diameter × 3 + 2 cm) has proved useful [11]. However, the majority of tubes which were displaced accidentally were of adequate length as judged by the formula quoted above; in four patients they were noted to be a little long. Few patients were paralysed, so that if accidental extubation occurred, spontaneous ventilation continued, reducing the risk of hypoxic damage. This complication, often occurring during weaning from ventilatory support when the patients did not require re-intubation, was recognized rapidly. In five of the patients who suffered accidental extubation, the tube had been noted previously on x-ray to be short. However, because the patient was thought to be nearly ready to undergo extubation of the trachea, the decision had been made not to change it for a longer one.

Forty-two (40 %) of the patients who exhibited accidental extubation were neonates, and 88 (84 %) were less than 1 yr old. This complication occurred in some infants on more than one occasion. Accidental extubation was seen in 3–4.9 % of admissions per annum in this study; this appeared to increase in 1988. There was no obvious reason for this increase, which occurred mainly in the cardiac unit. On average, accidental extubation occurred only once every 167 intubation days. The accidental extubation rate was higher on the respiratory/medical ward (every 125 intubation days) than on the other wards (every 179 days on the cardiac ward and 185 days on the neonatal surgical ward). This may be partly because of the more frequent use of infusions of opioids in postoperative patients. There was only one accidental extubation on the neurosurgical ward, where the use of neuromuscular blocking agents was more common, but this ward accounted for only 2 % of total intubation days.

Accidental extubation is a risk which is particularly likely to occur during weaning from the ventilator.

Tube blockage

The incidence of tube blockage varied between 1.6 % and 3.5 % (mean 2.6 %), despite the use of high humidity and the regular instillation of normal saline down the tube followed by suction. In more than 90 % of patients, the blockage necessitated immediate replacement of the tube.

Over 80 % of blockages occurred with a tube of 3.5 mm diameter or less. Meticulous nursing care is required if these small tubes are to be kept patent, and it is important that the suction catheter is passed through the tube completely. Therefore, its length should be noted. It is possible that the reluctance of staff to disturb the smallest, sickest infants by too frequent suctioning may have been responsible in part for the higher incidence of tube blockage in this group. The incidence of blockage was greater in the respiratory/medical ward (every 156 days) than in other wards (every 179 days in the cardiac ward and 218 days in the neonatal surgical ward), probably because these patients tended to have more secretions. In 1985, some patients were still being nursed in areas such as the infectious disease ward, outside the main intensive care areas of the hospital, partly because the relevant nursing skills were thought to be most appropriate for individual cases on such wards, but partly because of the reluctance of individual consultants to refer patients to the intensive therapy wards. The incidence of tube blockage occurred twice as frequently in outside wards, and provided useful factual evidence with which to convince the hospital to prohibit the use of artificial ventilation outside designated intensive therapy areas. There were no tube blockages on the neurosurgical ward.

Stridor on extubation

Although this complication occurred in 44 patients, it was severe enough to require re-intubation in only 21—less than 1 % of the total series. This is in contrast with early reports which described an incidence of post-intubation stridor of 4–10 % [3, 12] and an incidence of subglottic stenosis of 2–4 % [4–7]. This improvement probably resulted from the fact that the tube is always small enough to allow a slight leak of air around it when positive pressure is applied [13]. In the 3-yr period, only six tubes had to be changed because there was no leak around them, although in the same period 58 tubes had to be changed because the leak was excessive. This suggests that, at least in this department, Stocks' message has been taken seriously.

Abbott [3] showed that sub-clinical post-intubation laryngeal damage could be identified at laryngoscopy, even in patients without stridor, but the clinical significance of this finding is debatable. None of the patients who were admitted on subsequent occasions and required tracheal intubation was noted to have evidence of subglottic narrowing; however, elective post-intubation laryngoscopy was not felt justifiable in patients without symptoms.

The number of patients requiring re-intubation for stridor has declined progressively during the period of the study, from 10 in 1985 to two in 1988. None of the patients who developed stridor was a neonate, although 11 (25 %) were younger than 1 yr. Fourteen (32 %) had pre-existing laryngeal pathology (table IX), two with haemangiomata involving the airway requiring tracheotomy. Ten patients, including two of those with laryngeal pathology, had been intubated at the referring hospital before transfer to Great

Ormond Street, and in two patients a Cole pattern tube, which is known to cause laryngeal damage [14], had been used. The incidence of stridor in patients without laryngeal pathology, whose trachea had not been intubated before transfer, was 50% of the overall incidence.

The average duration of intubation in patients who developed stridor was 6.5 days, varying between 12 h and 29 days. There appeared to be no relationship between duration of intubation or repeated intubation and the incidence of stridor.

Nasal ulceration

There were six patients with marked nasal ulceration over the 3-yr period, although lesser degrees of temporary nasal erythema were more common. This complication may have been under-reported. The effect of the ventilator tubing pulling the Tunstall frame upwards against the nares was the main cause; other relevant factors were the presence of sepsis, hypotensive periods, or both, when peripheral perfusion may have been compromised. Careful fixation of the connector away from the nose and protection of the alae with stoma adhesive or foam-backed dressing may reduce the incidence of this complication.

Bronchial intubation

The initial tube was too long in 59 patients, although in only four did bronchial intubation occur. One of these was a 1.6-kg neonate with bronchopulmonary dysplasia in whom a tube of 10 cm length had been used. A substitute tube of 9 cm length came out accidentally 21 days later, demonstrating the fine balance between a tube being too long or too short in small infants.

Multiple complications

Multiple complications occurred in several children, most of whom were infants. The commonest association was blockage of the tube with accidental extubation. This probably reflects the fact that both these complications are more common in this age group.

Indications for tracheotomy

One hundred and eleven patients in this study required tracheotomy (4%). The majority (63) had pre-existing upper airway problems, and the remainder required very long term ventilatory support either for medical problems or following surgical repair of such conditions as congenital diaphragmatic hernia with severe pulmonary hypoplasia, or with diaphragmatic paralysis following cardiac surgery. Othersen [15] considered that there was an overdependence on long term nasotracheal intubation in children and advocated early tracheotomy. However, this study shows that long term tracheal intubation can be managed with an acceptably low incidence of complications, and that tracheotomy has virtually no role in patients without pre-existing upper airway pathology for the first 3–6 weeks. If, after this time or even earlier, it is clear that there is no likelihood of an end to the period of airway support in the near future, tracheotomy should be considered, as it has considerable advantages for very long term airway support, particularly in terms of the emotional development of the child. Tracheotomy has been shown previously to be a relatively safe procedure in infants and young children [16, 17]. There were no deaths in any of our patients who required tracheotomy. However, complications have been reported frequently, especially in young infants and patients in whom the pathology is initially infective [18, 19].

Implications for future patient care

Computerized monitoring of complication rates over the past 4 years has had several benefits. It has ensured that all patient data sheets are stored with 100% retrieval, thus allowing continuity of care both on a day-to-day basis and for longer term follow-up. Information is available rapidly in the event of repeated admissions, and the close monitoring of both morbidity and mortality is encouraged, together with the assessment of the effects of changes in management. Internal audit of the complication rates year by year provides an incentive to the members of the department to devise ways of trying to minimize their incidence, and permits early monitoring of any sudden increase in complications in any of the main intensive care areas. Data collected in this database are presented regularly at departmental mortality and morbidity meetings, and have generated useful discussions between the physicians and anaesthetists in charge of the intensive therapy units in the hospital.

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EFFECTS OF ALFENTANIL AND FENTANYL ON INDUCTION OF ANAESTHESIA IN PATIENTS WITH SEVERE PREGNANCY-INDUCED HYPERTENSION

C. C. ROUT AND D. A. ROCKE

SUMMARY

Forty patients with severe pregnancy-induced hypertension presenting for Caesarean section under general anaesthesia were allocated randomly to receive either fentanyl 2.5 $\mu g\ kg^{-1}$ or alfentanil 10 $\mu g\ kg^{-1}$ as part of the anaesthetic induction sequence. In all patients, the cardiovascular response to tracheal intubation was measured. Both drugs attenuated the response equally but did not abolish it in all patients. Alfentanil 10 $\mu g\ kg^{-1}$ is a suitable alternative to fentanyl 2.5 $\mu g\ kg^{-1}$ for patients with pregnancy-induced hypertension.

KEY WORDS

Anaesthesia. obstetric. Analgesics: alfentanil, fentanyl. Intubation, tracheal: cardiovascular response.

Although there has been a steady decrease in hypertension as a cause of maternal mortality in England and Wales, the number of cerebrovascular deaths in the latest triennium, 1982–84, was the greatest since the reports began [1]. The latest Report on Confidential Enquiries into Maternal Deaths in England and Wales emphasized the high incidence (72 %) of substandard care in hypertensive patients and recommended that, as pre-eclampsia of life threatening severity is now rare, regional teams with special expertise should be formed to provide advice or assume management [1, 2]. The problem of pregnancy-induced hypertension (PIH) appears to be increasing in the developing world [3] and in our own institution PIH is the greatest cause of maternal death in a society in which maternal mortality rates are 10 times higher than in the developed world [4]. In our population, patients presenting with either PIH or pregnancy-aggravated hypertension (PAH) represent 5–12 % of all deliveries, 50 % of which require delivery by Caesarean section [5].

As cerebrovascular accident is the commonest cause of death in PIH, attention should be directed towards an anaesthetic technique that provides haemodynamic stability throughout the surgical procedure and, unless contraindicated, extradural analgesia is probably the preferred technique [6]. However, under circumstances in which the mother has suffered a convulsion (eclampsia) or there are problems with maternal coagulation or fetal distress, general anaesthesia may be necessary [7]. If general anaesthesia is used for patients with PIH or PAH, haemodynamic stability must be provided, particularly during the period of tracheal intubation when patients are at greatest risk [8]. Several methods have been advocated to obtund the pressor response to intubation, including administration of opioids before induction of anaesthesia. The ultra short-acting opioid alfentanil has been shown to obtund the pressor response to tracheal intubation in the normal pregnant patient [9], but to our knowledge has not been studied in the hypertensive pregnant patient. In this study we have compared the effects of alfentanil 10 $\mu g\ kg^{-1}$ and those of fentanyl 2.5 $\mu g\ kg^{-1}$ as part of the anaesthetic induction technique on the pressor response to trachael intubation in patients presenting with severe PIH.

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PATIENTS AND METHODS

The study was undertaken with the approval of the Ethics and Professional Standards Sub-Committee of the Faculty of Medicine, University of Natal. Forty patients undergoing emergency Caesarean section were studied. All patients were older than 25 yr, were multiparous and had presented with a sustained diastolic arterial pressure >110 mm Hg with or without significant proteinuria, peripheral oedema, or both.

Following diagnosis, patients were admitted to the labour ward, where a central venous catheter (for measurement of central venous pressure (CVP)) and a 14-gauge peripheral infusion cannula were inserted under local anaesthesia. Hypertension was treated by the obstetric team and CVP was corrected to 4–6 cm H_2O when necessary by infusion of crystalloids. Patients were transferred to the operating theatre in the left lateral position and on arrival were given 30 ml of sodium citrate 0.3 mol litre^{-1} orally and positioned on the operating table with a wedge (15°) under the right buttock. All patients received metoclopramide 10 mg i.v.

An electrocardiograph was connected and the ECG (Lead II) monitored continuously. A radial artery cannula was inserted under local anaesthesia and connected to an HP78034A monitoring system with twin-channel hard copy recorder. Whilst the patients were breathing air, arterial blood was withdrawn for baseline analysis of blood-gas tensions and acid–base status. Heart rate and arterial pressure were allowed to stabilize and preoxygenation with 100% oxygen commenced via a face mask.

Patients were given an i.v. injection of glycopyrrolate 0.2–0.4 mg and droperidol 5 mg, 5 min before induction. Particular attention was paid to the level of consciousness, which was monitored continuously by eliciting responses to verbal questioning. Patients were allocated randomly to receive either fentanyl 2.5 μg kg^{-1} or alfentanil 10 μg kg^{-1}. Induction of anaesthesia was undertaken approximately 3 min after fentanyl and 1 min after alfentanil was administered.

Induction consisted of lignocaine 1 mg kg^{-1}, followed by etomidate 0.3 mg kg^{-1} and suxamethonium 1 mg kg^{-1} given in rapid sequence. Cricoid pressure was applied when consciousness was lost during the administration of etomidate or if there was any impairment of conscious level preceding induction. The trachea was intubated with a cuffed tracheal tube approximately 1 min after administration of suxamethonium and the time marked on a recorder. Maintenance of anaesthesia was with enflurane up to 0.8% and 50% nitrous oxide in oxygen; the patient's lungs were ventilated to Pa_{CO_2} 4.3 kPa. Neuromuscular block was produced with alcuronium 150 μg kg^{-1} or intermittent suxamethonium in those patients who had received magnesium sulphate as part of the antihypertensive therapy.

An infusion of syntocinon was administered after delivery and in the alfentanil group additional analgesia was provided with further administration of alfentanil, pethidine or papaveretum. Glycopyrrolate and neostigmine were used to antagonize residual neuromuscular block at the end of surgery in those patients who had received a non-depolarizing neuromuscular blocking agent.

Maternal arterial blood was taken immediately before delivery and neonatal blood samples obtained at delivery from a double-clamped segment of umbilical cord. Samples were analysed using a semi-automatic blood-gas analyser (Corning 170 pH/blood-gas analyser). A record was made of the time from induction to delivery (I–D) and of the time from uterine incision to delivery (U–D).

All neonates were examined immediately after delivery by staff experienced in neonatal resuscitation. Assessment of the time to sustained ventilation (TSV) was measured and a modified Apgar (minus colour) score (0–8) obtained at 1 and 5 min. When necessary, naloxone 0.01 mg kg^{-1} was administered in divided doses i.m., i.v. or both. All neonates were transferred to the neonatal intensive care unit as soon as possible.

The record of ECG and arterial pressure was reserved for subsequent analysis. Measurements of pre-induction, post-induction and peak post-intubation values of heart rate and systolic and diastolic arterial pressures were analysed. Pre-induction and post-induction values were defined as average values over a 15-s period in which values varied by less than 10% from the average. There were two patients with eclampsia in each group. Comparisons between and within groups were undertaken using Student's t test with a significance level of $P < 0.05$ (two-tailed). Non-parametric data were compared using chi-square analysis. Data are presented with both t and P values as appropriate.

TABLE I. *Group data (mean* SD*)) (unpaired* t *test). ns = Not significant*

	Fentanyl group	Alfentanil group	*t*	*P*
Maternal age (yr)	30.5 (4.6)	33.8 (5.1)	2.14	0.04
Maternal weight (kg)	82.1 (15.6)	80.8 (12.3)	0.27	ns
Gravid status	4.4 (1.70)	5.5 (2.27)	1.73	ns
Gestation (weeks)	35.8 (2.8)	33.4 (4.1)	2.1	0.04
Neonatal weight (kg)	2.17 (0.6)	1.86 (0.8)	1.4	ns
Induction to delivery time (I–D) (min)	13.5 (3.9)	13.4 (3.2)	0.08	ns
Uterine incision to delivery (U–D) (s)	97.9 (47.2)	86.9 (36.1)	0.8	ns
Intubation time (s)	57.4 (18.4)	70.6 (14.6)	2.5	0.016

TABLE II. *Patients receiving preoperative medication (no. of patients). No significant differences (methyldopa, chi square = 1.62)*

	Fentanyl group	Alfentanil group
Magnesium sulphate	9	8
Hydralazine	15	15
Methyldopa	11	7
Phenobarbitone	12	12
Diazepam	2	3
Nifedipine	2	2
Practolol	1	0
No treatment	0	2

RESULTS

Patients in the alfentanil group were significantly older ($P = 0.04$) and had significantly more premature neonates ($P = 0.04$). The differences in gravid status and birth weight between the two groups were not statistically significant. Mean intubation time was significantly longer in the alfentanil group ($P = 0.016$). There were no differences in maternal weight, I–D or U–D times between the two groups (table I). There were no significant differences in preoperative medication between the two groups (table II).

The difference in mean heart rate between the groups before induction was not statistically significant ($P = 0.06$) (table III). One patient in the fentanyl group underwent β-block before induction, but the preinduction heart rate in this patient was 130 beat min^{-1}. There was no significant change in mean heart rate after induction in each group, but after tracheal intubation both groups showed a significant increase in heart rate compared with preinduction values. There was a significant ($P < 0.001$) decrease in systolic arterial pressure after induction in both the groups, followed by a significant increase after tracheal intubation. However, there were no statistically significant differences in mean systolic arterial pressure, before induction and after intubation, within or between the groups. Both groups showed a small (10.9 and 9.3 mm Hg), but significant increase in mean diastolic pressure following tracheal intubation, with no differences between the two groups.

There were eight neonatal deaths in the study: five in the alfentanil group (mean gestational age 30 weeks, mean weight 1.04 kg, range 0.55–1.5 kg) and three in the fentanyl group (mean gestation 32 weeks, mean weight 1.17 kg, range 0.95–1.45 kg). All deaths were related to prematurity or growth

TABLE III. *Heart rate, systolic and diastolic pressures (mean* (SD*)). Comparison of pre-induction with post-intubation values using paired* t *test. ns = Not significant. Between group comparisons using unpaired* t *test showed no significant differences*

	Pre-induction	Post-induction	Post-intubation	*t*	*P*
Heart rate (beat min^{-1})					
Fentanyl	98 (19.2)	102 (16.9)	114.3 (19.1)	4.75	1.39E-4
Alfentanil	108.8 (15.3)	106.9 (13.8)	118.3 (16.0)	2.4	0.027
Systolic arterial pressure (mm Hg)					
Fentanyl	170.2 (27.6)	152.1 (26.2)	180.8 (37.2)	1.78	ns
Alfentanil	173.9 (21.3)	151.7 (18.8)	181.9 (33.0)	1.20	ns
Diastolic arterial pressure (mm Hg)					
Fentanyl	103.3 (14.4)	98.2 (14.6)	114.2 (21.1)	2.87	9.8E-3
Alfentanil	103.5 (13.1)	95.9 (14.2)	112.8 (20.3)	2.46	0.024

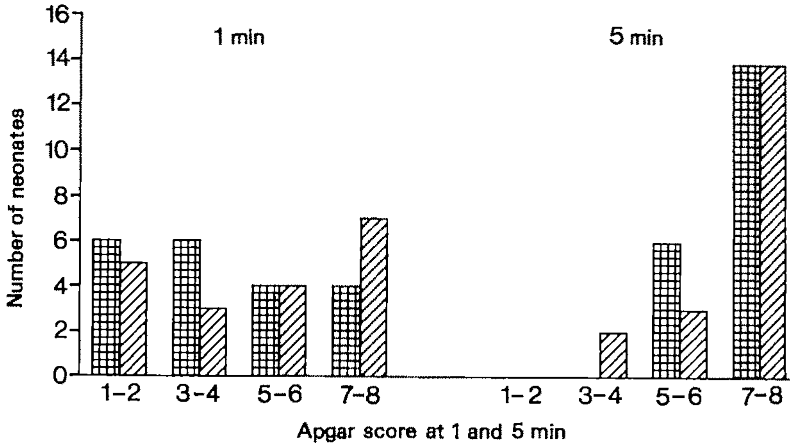

FIG. 1. Modified Apgar (minus colour) scores at 1 and 5 min. ⊞ = Fentanyl; ▨ = alfentanil.

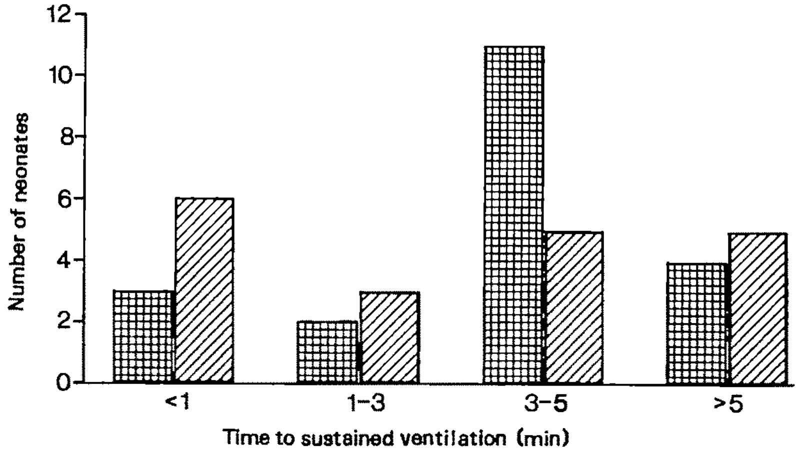

FIG. 2. Time to sustained ventilation after fentanyl (⊞) or alfentanil (▨).

retardation, or both, with the development of hyaline membrane disease. Modified Apgar scores at 1 and 5 min and TSV are shown in figures 1 and 2. One infant in the alfentanil group was excluded from the results because of extreme prematurity (22 weeks) and low birth weight (550 g), with no effort being made to resuscitate. There were no significant differences between the two groups.

Maternal and neonatal blood-gas data are shown in table IV. Intraoperative samples were not obtained in two mother–neonate pairs in the alfentanil group, and umbilical arterial sampling proved impossible in one pair in the fentanyl group. There was no significant difference between the two groups in maternal blood-gas tensions. Umbilical arterial $P\text{O}_2$ was significantly greater in the fentanyl group ($P = 0.02$).

DISCUSSION

Control of the pressor response to tracheal intubation is an essential part of any general anaesthetic technique in severe PIH [10]. In a previous study from this department, a technique based upon nitrous oxide and a volatile agent failed to provide a safe technique, applicable to all mothers with PIH [11] and it was confirmed that increasing age and parity were significant prog-

TABLE IV. *Maternal and neonatal blood-gas and acid–base status at delivery (mean (SD)).* ‡ n = *18*; † n = *19*. *BE = Base excess.* * $P < 0.05$

	Fentanyl		Alfentanil
Maternal baseline			
pH	7 42 (0.06)		7 44 (0 06)
Pa_{CO_2} (kPa)	3.69 (0.39)		3.57 (0.47)
Pa_{O_2} (kPa)	14.1 (1.66)		13.4 (1.41)
BE (mmol litre^{-1})	−3.46 (2.35)		−2.85 (3.11)
Maternal delivery (FI_{O_2} 0.5)			
pH	7.43 (0.10)		7.39 (0.07)‡
Pa_{CO_2} (kPa)	3.99 (0.39)		4.15 (0.81)‡
Pa_{O_2} (kPa)	29.21 (6.62)		24.27 (7.56)‡
BE (mmol litre^{-1})	−3.62 (1.95)		−4.11 (3.42)‡
Umbilical vein			
pH	7.28 (0.12)		7.29 (0.06)‡
P_{CO_2} (kPa)	6.05 (1.34)		6.31 (0.89)‡
P_{O_2} (kPa)	3.81 (1.17)		3.21 (1.12)‡
BE (mmol litre^{-1})	−4.95 (4.26)		−3 73 (3.10)‡
Umbilical artery			
pH	7 22 (0.13)†		7.25 (0.06)‡
P_{CO_2} (kPa)	7.15 (1.51)†		7.13 (0.92)‡
P_{O_2} (kPa)	2.21 (0 81)†	*	1.61 (0.68)‡
BE (mmol litre^{-1})	−5.76 (4.97)†		−4.57 (3.23)‡

nostic indicators. It was suggested that for the older, multiparous patient with PIH a different anaesthetic approach should be used, particularly as a more severe pressor response to intubation may be expected. Our study has thus been confined to the elderly multigravid patient with severe hypertension.

One method of obtunding the pressor response to a rapid sequence induction is by using an opioid such as fentanyl or alfentanil. Fentanyl 200 µg, given in divided doses in an elderly, multiparous group of patients presenting for Caesarean section has been found to obtund the hypertensive response to laryngoscopy in most patients [12]. Whilst maternal safety is the overriding consideration, drug-induced neonatal depression should be minimal and alfentanil may be more appropriate in view of its physicochemical properties.

Alfentanil has been used to obtund the pressor response to tracheal intubation in both the pregnant [9] and non-pregnant patient [13]. Comparison between fentanyl and alfentanil in non-pregnant patients showed that alfentanil 15 µg kg^{-1} was effective in suppressing the increase in arterial pressure subsequent to tracheal intubation, and 30 µg kg^{-1} also suppressed the increase in heart rate, whereas fentanyl 5 µg kg^{-1} suppressed both [13]. However, the effects of alfentanil were of shorter duration than the effects of fentanyl. In the normotensive patient undergoing elective Caesarean section, alfentanil 10 µg kg^{-1} is effective in modifying the arterial pressure and heart rate response to tracheal intubation [9].

The present study showed that alfentanil 10 µg kg^{-1} was as effective as fentanyl 2.5 µg kg^{-1} when used in combination with other agents in obtunding the pressor response to tracheal intubation and may be considered as an appropriate alternative. However, both groups showed an increase in heart rate and diastolic pressure following tracheal intubation and, although mean increases in heart rate of 16 beat min^{-1} (fentanyl), 11 beat min^{-1} (alfentanil) and in diastolic pressure of 11 mm Hg (fentanyl) and 8 mm Hg (alfentanil) may not be considered clinically significant, there was wide variation. Maximum changes of 45 beat min^{-1} (fentanyl), 47 beat min^{-1} (alfentanil) and 43 mm Hg (fentanyl), 32 mm Hg (alfentanil) were observed and were considered to be clinically significant in the individual patients.

Although there were no significant differences between the groups in pressor response, this must be viewed in the context of group comparability. We consider the PIH in the alfentanil group to have been more severe, in that those patients were older and delivered neonates of lower gestational age, the latter in relation to earlier termination of pregnancy in maternal interests.

The overall neonatal mortality in the study was

20%, which included one death at 22 weeks gestation. This is comparable to the mortality rate of 15% reported by Lawes and colleagues [12] and reflects the severity of the disease and the high incidence of premature delivery of low birth weight babies. None of the deaths could be attributable to the anaesthetic technique. As expected, neonatal mortality was not related to either modified Apgar scores or TSV. Neonates who died had significantly smaller mean birth weight (1.09 kg) than survivors (2.25 kg). There were no significant differences between the groups in the clinical condition of the neonates as assessed by modified Apgar scores and TSV.

The lesser fat solubility of alfentanil might be of advantage in reducing the rate of placental transfer in comparison with fentanyl, as would its increased protein binding [14], although decreased ionization at pH 7.4 (pK_a 6.5) would tend to increase placental transfer. The plasma protein largely responsible for binding alfentanil is the alpha-1 acid glycoprotein fraction [15]. This protein may be found in lesser concentrations in the fetus [16] leading to a greater fraction of unbound drug in the fetal circulation, and perhaps greater neonatal depression if delivery occurs at peak maternal plasma concentrations of drug. Although there have been a limited number of studies it appears that the calculated [17] and measured [14] unbound maternal and fetal plasma concentrations of alfentanil are similar. However, when maternal concentrations of free drug begin to decrease, back transfer from the fetus should be rapid. Following a 10-min infusion of alfentanil 50 $\mu g\ kg^{-1}$ in the gravid ewe, transfer back has been demonstrated within 6 min of stopping the infusion [18]. The shortest induction to delivery time in the alfentanil group in our study was 9 min. Transfer back of fentanyl appears not to occur [18].

The only significant difference found in blood-gas analysis was a lesser umbilical arterial P_{O_2} in the alfentanil group. Umbilical venous to arterial oxygen gradients were identical in the two groups (1.6 kPa), which suggests that the difference was caused by placental oxygen supply rather than altered fetal demand. The difference in mean maternal oxygen arterial tension between the two groups at delivery (4.5 kPa), while not statistically significant ($P = 0.058$), may be reflected in umbilical venous oxygen tensions. Neonatal demise was not related to umbilical blood values.

In addition to an opioid, the induction sequence included other agents which could play a role in obtunding the pressor response to tracheal intubation, including droperidol [19], lignocaine [20] and magnesium [21]. Magnesium sulphate has been shown to obtund the adrenergic response to tracheal intubation in hypertensive parturients. Seventeen patients in this study received magnesium sulphate therapy before operation (eight alfentanil, nine fentanyl). Two-way analysis of haemodynamic data revealed no influence of magnesium. It is possible that magnesium concentrations were not in the therapeutic range, as they were not monitored in this study [22].

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PHARMACOKINETICS OF AN INFUSION OF PROPOFOL DURING CARDIAC SURGERY

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SUMMARY

We have measured whole blood concentrations and pharmacokinetics of propofol administered as a constant rate infusion during cardiac surgery. Ten patients undergoing elective cardiac surgery involving cardiopulmonary bypass (seven myocardial revascularization and three aortic valve surgery) received a continuous infusion of propofol 4 mg kg^{-1} h^{-1} to supplement alfentanil analgesia. Whole blood propofol concentrations were measured by high pressure liquid chromatography. A concentration greater than 1 µg ml^{-1} was achieved within 15 min of starting the infusion and remained constant throughout surgery. Volume of distribution, clearance and terminal half-life were similar to those found in non-cardiac patients.

KEY WORDS

Anaesthetics, intravenous: propofol. Pharmacokinetics: propofol.

High doses of opioid drugs have been advocated as the sole anaesthetic agent for cardiac surgery [1, 2]. However, they may cause prolonged postoperative respiratory depression and, when used alone, there is a possibility of intraoperative awareness [3]. The use of a moderate dose of opioid supplemented by a hypnotic agent is a recognized solution to these problems [4]. Propofol has a pharmacokinetic profile which makes it suitable for both induction of anaesthesia and administration by continuous infusion. When used for induction of anaesthesia, propofol 2.5 mg kg^{-1} produces hypotension secondary to vasodilatation [5, 6]—a property undesirable in cardiac patients. However, an infusion of propofol is associated with less haemodynamic instability [7].

The aims of this study were: to establish that the dose of propofol infused routinely for cardiac surgery in our centre was sufficient to produce blood concentrations greater than the 1 µg ml^{-1} at which patients wake up after non-cardiac surgery [8, 9]; to determine if concentrations changed during cardiopulmonary bypass (CPB); and if the acute changes during and after CPB altered the pharmacokinetic values for propofol from those in non-cardiac patients.

PATIENTS AND METHODS

After local Ethics Committee approval was granted, written consent was obtained from 10 patients (mean age 46 yr (range 17–62 yr); mean weight 84 kg (range 60–127 kg)) undergoing elective cardiac surgery involving CPB (seven myocardial revascularization, three aortic valve surgery). None had biochemical evidence of hepatic or renal impairment and all had angiographic evidence of good left ventricular function with an estimated ejection fraction greater than 0.5. Established cardiac drug therapy was continued until surgery and premedication of papaveretum 15–20 mg and hyoscine 0.3–0.4 mg was given i.m. 1 h before anaesthesia.

Peripheral venous, radial arterial and internal jugular venous cannulation were performed under local anaesthesia before induction of general anaesthesia. After 3 min of preoxygenation, anaesthesia was induced over 2 min with i.v. midazolam 2–3 mg and alfentanil 50 µg kg^{-1}. Muscle relaxation was produced and maintained with pancuronium 0.15 mg kg^{-1}, the trachea intubated

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and the lungs ventilated to normocapnia with oxygen. Following induction, a zero-order i.v. infusion of propofol 4 mg kg^{-1} h^{-1} was started via a dedicated peripheral i.v. cannula using a syringe pump (MS 2000, Graseby Medical, Watford) and continued until the patient arrived in the intensive care unit. Analgesia was maintained by an i.v. infusion of alfentanil 60 μg kg^{-1} h^{-1} continued until the start of CPB and a supplement of alfentanil 50 μg kg^{-1} was given over 2 min at skin incision. A membrane oxygenator (M2000, Shiley) primed with Plasmalyte solution 2000 ml, 8.4% sodium bicarbonate 100 ml and 20% mannitol 100 ml was used for the CPB, during which patients were cooled to a nasopharyngeal temperature of 28 °C. An infusion of glyceryl trinitrate 1–5 mg h^{-1} was started on rewarming and continued until the end of surgery. No patient required inotropic support following surgery. The duration of propofol infusion from induction to CPB, during CPB and from the end of CPB to the end of infusion were recorded.

Blood samples of 5 ml were obtained from the radial artery cannula at 15, 20 and 30 min and subsequently at 15-min intervals after the start of infusion until CPB; at 5, 10 and 15 min and subsequently at 15-min intervals during CPB; and at 5, 10, 15, 20 and 30 min and subsequently at 15-min intervals after CPB until the end of the infusion. Additional samples were taken immediately before the start and the end of CPB to provide a baseline for the samples taken after these events. When the patient arrived in the intensive care unit a blood sample was taken, propofol was discontinued and further samples were taken at 5, 10, 15, 30, 45, 60, 75, 90 and 120 min and at 4-h intervals until 24 h after the end of the infusion.

Samples were collected in tubes containing potassium oxalate and stored at 4 °C until assay of total whole blood concentration of propofol by high pressure liquid chromatography. The method conforms largely to that described previously [10], with the modifications that the samples were extracted into a 75:25 cyclohexane:hexane solution and dried at 40 °C under oxygen-free nitrogen. The lower limit of detection was 0.02 μg ml^{-1}. The inter-study coefficient of variation of the assay was 4% and intra-study coefficient of variation was 1.97%. These were not affected by the drug concentration within the range measured. The extraction recovery was greater than 95%.

Analysis of data

The total dose of propofol administered (DOSE) was calculated from the infusion rate and duration of infusion and a curve of whole blood concentration of propofol against time was drawn for each patient, thus allowing individual pharmacokinetic values to be derived. The mean concentration for the whole group at each of the sampling times was determined and curves of mean whole blood concentration against time were constructed for the intraoperative and early postoperative periods. Changes in concentrations during and after bypass with time were tested by analysis of variance and a P value of less than 0.05 was accepted as significant.

Non-compartmental analysis of the data for each patient was made by the statistical moments theory using the trapezoidal rule [11] and from this the area under the whole blood concentration ($C(t)$) against time curve to infinity (AUC) and the $C(t)$ × time (t) against time curve to infinity (AUMC) were measured. The mean residence time (MRT) corrected for the duration of infusion (T) was calculated using the formula:

$$\mathrm{MRT} = \mathrm{AUMC}/\mathrm{AUC} - 1/2T$$

The characteristics of the terminal part of the decay curve were used to derive the elimination half-life ($T_{\frac{1}{2}}$el) and constant (Kel). Clearance (Cl) and volume of distribution (V) of propofol for each patient were calculated using the formulae:

$$Cl = \text{DOSE}/\mathrm{AUC} \text{ and } V = Cl \times \mathrm{MRT}$$

RESULTS

The mean time from induction to CPB was 61.3 min (range 36–102 min). The target propofol concentration of greater than 1 μg ml^{-1} was achieved within the first sampling time at 15 min (fig. 1). The concentration remained greater than this with only a small increase throughout the period before CPB. The mean time of CPB was 87.7 min (range 39–126 min), during which patients were cooled to 28 °C and rewarmed subsequently to 37 °C. At the onset of CPB, no reduction in concentration of propofol was detected and values remained steady during CPB.

The mean time of infusion following CPB was 62.6 min (range 30–104 min) and nasopharyngeal temperature was maintained at 36–37 °C. Fol-

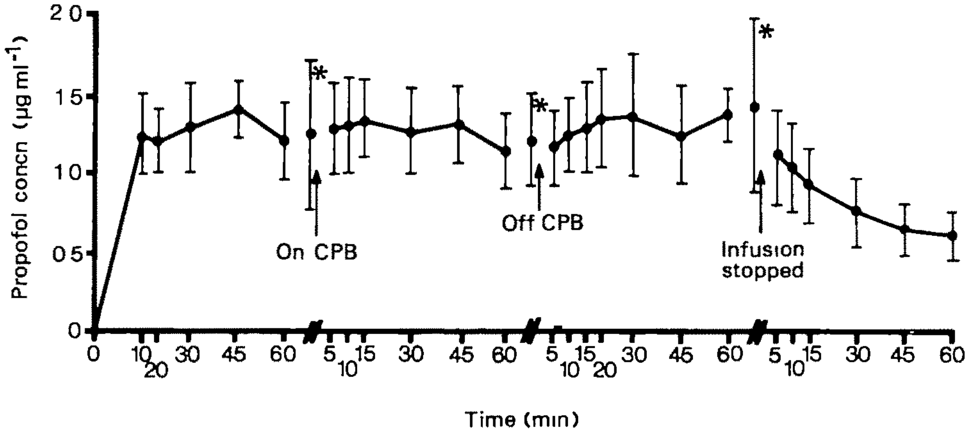

FIG. 1. Total whole blood concentrations of propofol during an infusion of 4 mg kg^{-1} h^{-1} in the times before, during and after cardiopulmonary bypass (mean, SD). * Mean of additional samples taken immediately before CPB, before stopping CPB and before stopping the infusion.

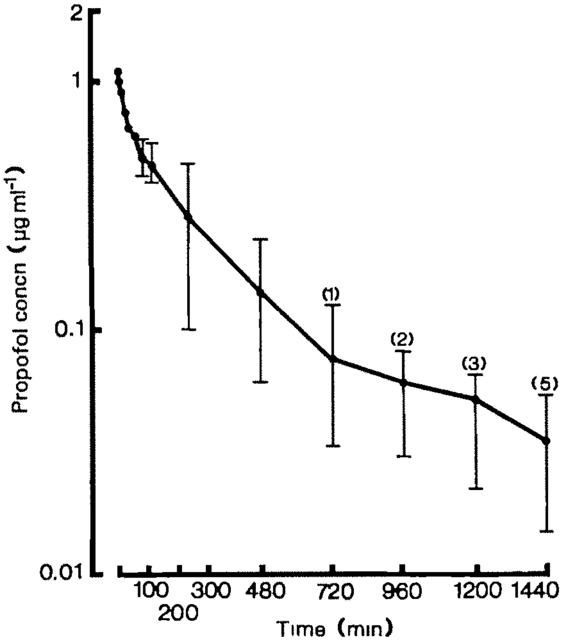

FIG. 2. Log total whole blood concentrations of propofol *vs* time after infusion (mean (+range after 90 min)). Number of samples below the lower limit of detection is indicated in parentheses.

lowing CPB there was, again, no significant change in concentration of propofol (fig. 1).

Mean total infusion time was 211.5 min (range 137–281 min). After stopping the infusion there was a rapid decline in whole blood concentration of propofol, and by 30 min it was less than 1 μg ml^{-1} (fig. 2).

The mean (SD) derived pharmacokinetic data of the 10 patients were: *V* 626 (313) litre; *Cl* 2.23 (0.55) litre min^{-1}; $T_{\frac{1}{2}}el$ 356 (67) min; *K*el 0.00201 (0.00037) min^{-1}.

DISCUSSION

Propofol and alfentanil were delivered through a dedicated peripheral line to allow good mixing in venous blood before return to the right heart. It was accepted that delivery might be affected by poor peripheral perfusion during hypothermic CPB. However, when propofol is delivered centrally during open heart surgery it may be seen sometimes escaping into the pericardium in "milky" streams from leaks around the right atrial cannula.

In this laboratory, several different extraction solvents were investigated for more accurate results with lower coefficients of variation than the described methods. Of those tested, 75:25 cyclohexane:hexane gave the most accurate, cleanest peaks with the standard solutions. From investigations at different temperatures it was found that drying the solution at 40 °C under oxygen-free nitrogen gave no denaturing of the drug and the drying time was reduced considerably compared with that at ambient temperature.

Following the start of the zero order infusion of propofol, there was an initial fast increase in concentration, so that a whole blood concentration greater than 1 μg ml^{-1} was attained at 15 min, followed by a slower increase. However, in the limited time to CPB a steady concentration would not be achieved. The initial rate of increase in whole blood concentrations of propofol and the concentrations attained within the time period before CPB were faster than expected on the basis of pharmacokinetic principles, but were in agreement with a study of zero order infusions of propofol by Gepts and co-workers [10]. This may represent changes in *V* or $T_{\frac{1}{2}}$el in these patients during induction and early anaesthesia.

Propofol concentration was not altered by the onset of CPB. This was to be expected because the extra 2.2 litre of crystalloid added to the circulation was small compared with the volume of distribution into which propofol is rapidly distributed [8–10]. This finding is in contrast with those of Russell and co-workers [12] who detected a reduction in concentration at 2–10 min. These differences may arise because they sampled from the pump oxygenator during bypass, not from the radial artery, and because changes in the concentration of propofol in the bypass system and the patient may not be comparable at times of rapid volume change. Also, although the sampling times were not specified by Russell's group, they may have sampled sooner and more frequently than us. The whole blood concentration of propofol did not alter significantly during CPB, despite the presence of several factors which may alter drug disposition, including: altered regional blood flow secondary to hypothermia, vasoactive drugs and cessation of pulmonary blood flow causing a decrease in hepatic clearance, renal clearance and distribution volume; and haemodilution during CPB causing a decrease in protein binding and an increase in the distribution volume.

After CPB there was a non-significant increase in the concentration of propofol within the first 30 min, similar to that noted by Russell and co-workers [12]. This was probably because the concentration was increasing towards equilibrium before CPB and, despite the interruption, the increase was resumed after it. In addition, during CPB, propofol may have been sequestered in areas which were poorly perfused, such as the peripheries, lung and liver, and subsequently returned to the circulation to contribute to the increased concentrations.

Propofol was used as a hypnotic agent to supplement the analgesia provided by alfentanil. Previous studies in non-cardiac patients have shown that maintenance infusion rates of between 3.73 and 4.29 mg kg^{-1} h^{-1} [13–15], when combined with full regional analgesia, are associated with lack of awareness, and that patients wake up at whole blood concentrations of propofol about 1 μg ml^{-1} [7–9, 16]. In this study, after the first 15 min, the mean blood concentration of propofol throughout surgery exceeded 1 μg ml^{-1} and, when combined with the hypnosis of a papaveretum premedication and midazolam at induction, should have been adequate to provide hypnosis. Although on direct questioning, and in our clinical use of propofol infusions, no patient complained of awareness, more detailed evaluation is required.

The use of non-compartmental analysis of pharmacokinetic parameters for infusions of propofol has been validated in non-cardiac patients [10]. During cardiac surgery pharmacokinetic variables may change in the periods before, during and after CPB. However, the use of non-compartmental analysis was judged appropriate because all patients are subjected to each phase and it is the net effect that is important clinically. The *V* quoted is an overall volume of distribution, rather than that of equilibrium at steady state. It is clear that steady state was never achieved, as the duration of infusion was too short and the volume of distribution may have differed during the different phases. During CPB the addition and removal of crystalloid and blood, affecting plasma proteins and hence binding capacity, might be expected to affect the *V* of drugs. However, the mean *V* (626 litre) in this study was within the range reported in patients undergoing non-cardiac surgery (298–1008 litre) [8–10, 17] and presumably this is because the volumes of the fluid fluxes were small compared with the overall *V*. Propofol is known to be 88% metabolized by conjugation [18], mainly in the liver, and drugs with a high hepatic extraction ratio given i.v. are usually sensitive to factors that affect hepatic blood flow (e.g. CPB) and to a lesser extent hepatic enzyme activity (e.g. hypothermia); however, in this study the clearance (2.23 litre min^{-1}) remained within quoted limits (1.3–2.3 litre min^{-1}). With the high clearance, whole blood concentrations of propofol decreased rapidly after the infusion was stopped and by 30 min were less than 1 μg ml^{-1}. $T_{\frac{1}{2}}$el (356 min) was longer than that measured after bolus injections of propofol in surgical patients

(184–309 min) [8, 9], but was in agreement with that measured after infusions (227–403 min) [10].

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CARDIOVASCULAR EFFECTS OF DOXACURIUM, PANCURONIUM AND VECURONIUM IN ANAESTHETIZED PATIENTS PRESENTING FOR CORONARY ARTERY BYPASS SURGERY†

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SUMMARY

The cardiovascular effects of bolus doses of doxacurium 0.037 mg kg^{-1} were compared with those following equipotent doses of pancuronium (0.09 mg kg^{-1}) and vecuronium (0.075 mg kg^{-1}) and with those following high-dose doxacurium (0.075 mg kg^{-1}), in patients with coronary artery disease. Anaesthetic technique comprised premedication with lorazepam, papaveretum and hyoscine, induction with diazepam, fentanyl, thiopentone, atropine and suxamethonium, and the trachea was intubated. At least 20 min later, during stable nitrous oxide in oxygen anaesthesia, a single bolus of neuromuscular blocking drug was administered and the effects measured at 1, 5 and 10 min. There was a small decrease in heart rate following doxacurium 0.075 mg kg^{-1}, but no other significant or dose-related changes in mean heart rate, arterial pressure or cardiac index with doxacurium. Similar results were found following vecuronium, but the reduction in heart rate was more pronounced. In contrast, significant increases in mean arterial pressure, heart rate and cardiac index occurred after pancuronium.

KEY WORDS
Heart: Coronary artery surgery. Neuromuscular relaxants: doxacurium, pancuronium, vecuronium.

Pancuronium has been advocated as the skeletal muscle relaxant of choice during anaesthesia for coronary artery bypass graft (CABG) surgery [1]. However, in some patients its vagolytic and sympathomimetic effects may cause myocardial ischaemia [2, 3]. Vecuronium, a pancuronium analogue, produces little haemodynamic change in patients undergoing CABG surgery and this drug may be preferable in patients with limited cardiac reserve [4]. However, the use of vecuronium in these circumstances may be associated, in some patients, with marked bradycardia [5].

Doxacurium chloride (BW A938U) is a new non-depolarizing neuromuscular blocking agent. It has a long duration of action, comparable to that of pancuronium [6]. The administration of doxacurium appears to cause minimal changes in heart rate or arterial pressure [6, 7]. The present study was designed to compare the haemodynamic effects of single bolus doses of doxacurium, pancuronium and vecuronium in anaesthetized patients undergoing CABG surgery.

PATIENTS AND METHODS

After approval from the Committee on Safety of Medicines and the local Ethics Committee, we studied 36 ASA Class III or IV adult patients undergoing elective CABG surgery. Each patient gave signed informed consent. Angiograms of the patients were viewed before operation and left ventricular function was assessed as good, moderate or poor. Patients with valvular disease requiring surgery, with poor left ventricular function or critical narrowing of the left main

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coronary artery were excluded; other exclusions included a history of alcohol or drug abuse, clinically significant neuromuscular, hepatic, renal or psychiatric disease, exposure to histamine receptor (H_1/H_2) antagonists within 24 h before surgery, and a history of asthma. All routine cardiac and vasoactive medications were continued up to the morning of surgery. The first 27 patients studied were allocated randomly to receive an estimated $1.5 \times ED_{95}$ dose of doxacurium (0.037 mg kg^{-1}; group 1), pancuronium (0.09 mg kg^{-1}; group 2) or vecuronium (0.075 mg kg^{-1}; group 3); the final nine patients studied received an estimated $3 \times ED_{95}$ dose of doxacurium (0.075 mg kg^{-1}; group 4). Entry of patients into group 4 was deferred until the safety of doxacurium had been confirmed in the lower dose doxacurium group of patients (group 1).

Premedication consisted of oral lorazepam 2–4 mg, 90–120 min before and i.m. papaveretum 15–20 mg with hyoscine 0.3–0.4 mg 1 h before the patient arrived in the operating theatre, where they were monitored by ECG monitor (Kontron 304), and peripheral venous and radial artery cannulations were performed under local anaesthesia. Patients received i.v. diazepam 0.05–0.2 mg kg^{-1}. A triple-lumen thermodilution pulmonary artery flotation catheter (Spectramed 9002) and two central venous catheters were inserted under local anaesthesia. Measurements of arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressures were made using Gould Statham P23 pressure transducers precalibrated against a mercury column; these were recorded on a Kontron 304 chart recorder, with lead II of the ECG. Cardiac output measurements were made in triplicate using iced injectate and a Gould SP 1432 cardiac output computer. The evoked gated integrated compound electromyogram (EMG) of the adductor pollicis muscle in response to supramaximal train-of-four (2 Hz for 2 s) stimulation of the ulnar nerve (train frequency 0.05 Hz; stimulus duration 0.1 ms) was recorded using surface electrodes and a Datex Relaxograph. Following preoxygenation, anaesthesia was induced with additional i.v. diazepam 5–10 mg, fentanyl 500 µg and thiopentone 50–500 mg titrated to the individual response of each patient. Anaesthesia was maintained with 50% nitrous oxide in oxygen. Neuromuscular monitoring was calibrated and stabilized before administration of suxamethonium 1 mg kg^{-1}. Intubation was facilitated by spraying the larynx with 4% lignocaine. Administration of suxamethonium did not lead immediately to haemodynamic changes. However, at or shortly after laryngoscopy, seven of the first 10 patients developed profound bradycardia, requiring atropine. Subsequently, it was decided to administer atropine routinely at induction to all subjects. Following tracheal intubation, end-tidal carbon dioxide (Datex Normocap) was monitored, arterial blood-gas sampling was performed at regular intervals, and ventilation was adjusted to maintain normocapnia.

During stable anaesthesia, at least 15 min after intubation and following EMG confirmation of full recovery from suxamethonium-induced neuromuscular block, a single undiluted dose of doxacurium, pancuronium or vecuronium was injected as a rapid (5-s) bolus into a central vein. With the exception of cardiac output measurements, patients remained unstimulated from the time of intubation until at least 10 min following injection of the non-depolarizing neuromuscular blocking drug. After arrival of the patient in the operating theatre up to the end of the period of study, all patients received an i.v. infusion of compound sodium lactate solution 500 ml and up to 500 ml of Haemaccel.

Haemodynamic measurements were made immediately before induction of anaesthesia and at 5-min intervals after intubation of the trachea until vital signs were stable. The final recording in this sequence was defined as the baseline (pre-relaxant) recording, and immediately preceded administration of the non-depolarizing neuromuscular blocking agent. Further haemodynamic measurements were performed at 1, 5 and 10 min after administration of the non-depolarizing blocker. Variables recorded by later inspection of paper trace recordings included systolic (SAP) and diastolic (DAP) arterial pressures, heart rate (HR; average of five R–R intervals), mean central venous pressure (CVP), mean pulmonary artery pressure (PAP) and mean pulmonary capillary wedge pressure (PCWP).

All intravascular pressure measurements were made at end-expiration. Cardiac output measurements represent the mean of three readings. Estimates of mean arterial pressure (MAP) and cardiac index (CI) were calculated from the measured haemodynamic variables using standard formulae.

Repeated measures analysis of variance on log-transformed data was used to assess the significance of changes in haemodynaic variables over time. Haemodynamic data obtained before induction of anaesthesia were analysed independently using one-way analysis of variance and were not included in repeated measures analyses. Patient data were analysed using one-way analysis of variance or Fisher's exact test where appropriate. Comparisons were made between groups receiving equipotent doses of doxacurium, pancuronium or vecuronium (groups 1–3) and also between groups receiving doxacurium alone (groups 1 and 4). Statistical significance was taken at $P < 0.05$ (Huyhn and Feldt correction [8] for data analysed by repeated measures analysis of variance).

RESULTS

The four patient groups were comparable in age, weight, height, body surface area (BSA) (table I) and preoperative exposure to routine cardioactive medications (table II). There were no significant differences between groups in induction doses of fentanyl, thiopentone or diazepam, or in mean doses of atropine received after induction. The average times between anaesthetic induction or administration of atropine and administration of the non-depolarizing neuromuscular blocker were similar for all groups (table III).

There were no significant differences between groups 1, 2 and 3 or between groups 1 and 4 in haemodynamic variables before administration of the myoneural blocker (table IV). In analysing groups 1, 2 and 3, significant increases over time were observed in MAP, HR and CI after pancuronium, and a decrease in HR after vecuronium. After doxacurium 0.037 mg kg^{-1} (group 1) there were no significant changes with time in MAP, HR or CI. Significant decreases in CVP, PAP and PCWP were observed over time after equipotent doses of doxacurium, pancuronium and vecuronium, with no differences between groups. High dose doxacurium (0.075 mg kg^{-1};

TABLE I. *Preoperative patient data. (Mean (SD), or number of patients)*

	Group 1 (Doxacurium 0.037 mg kg^{-1})	Group 2 (Pancuronium 0.09 mg kg^{-1})	Group 3 (Vecuronium 0 075 mg kg^{-1})	Group 4 (Doxacurium 0.075 mg kg^{-1})
n	9	9	9	9
Age (yr)	52.7 (10.7)	53.9 (7.5)	50.2 (9.7)	55.8 (7.2)
Weight kg)	79.2 (6.3)	77.4 (9.0)	76.1 (12.4)	77.7 (8.6)
Height (cm)	173 (6)	172 (8)	174 (8)	176 (6)
BSA (m^2)	1.92 (0.07)	1.90 (0.14)	1 89 (0.19)	1.93 (0.14)
Sex (M:F)	9:0	9:0	8:1	8:1

TABLE II. *Number of patients receiving routine medications*

	Group 1	Group 2	Group 3	Group 4
β-Antagonist	6	7	7	7
Calcium channel blocker	8	5	6	7
Long-acting nitrate	4	5	5	4

TABLE III. *Induction data (mean (SD)).* †n = *8*; ‡ n = *7*

	Group 1	Group 2	Group 3	Group 4
Fentanyl (μg kg^{-1})	6.3 (0.5)	6.9 (1.4)	6.7 (2.3)	5.5 (1.7)
Thiopentone (mg kg^{-1})	1.6 (0.7)	1.9 (1.4)	1.9 (1.8)	1.3 (0.6)
Diazepam (mg kg^{-1})	0.11 (0.07)	0.09 (0.03)	0.14 (0.08)	0.15 (0.07)
Induction–blocker interval (min)	26.4 (4.7)	24.4 (4.2)	24.0 (1.8)	25.3 (1.8)
Atropine (μg kg^{-1})	4.3 (1.9)†	3.7 (2.3)‡	4.6 (2 1)	4.5 (1.0)
Atropine–blocker interval (min)	23.4 (7.8)	22.9 (6.5)	20.3 (4.8)	25.1 (1.8)

TABLE IV. *Mean systemic arterial pressure (MAP), heart rate (HR), cardiac index (CI), central venous pressure (CVP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP), before (baseline) and at 1, 5 and 10 min after administration of the myoneural blocker (mean* (SEM)*). Group 1 = doxacurium 0.037 mg kg*$^{-1}$*; group 2 = pancuronium 0.09 mg kg*$^{-1}$*; group 3 = vecuronium 0.075 mg kg*$^{-1}$*; group 4 = doxacurium 0.075 mg kg*$^{-1}$

		After myoneural blocker		
	Baseline	1 min	5 min	10 min
MAP (mm Hg)				
Group 1	73.9 (2.5)	72.8 (1.9)	75.4 (2.1)	74.6 (2.2)
Group 2	75.0 (2.4)	80.1 (1.5)	80.8 (1.9)	80.8 (1.6)
Group 3	81.7 (6.5)	79.4 (7.7)	80.4 (8.0)	80.0 (8.0)
Group 4	66.0 (2.8)	64.9 (3.0)	66.0 (3.2)	65.9 (2.9)
HR (beat min^{-1})				
Group 1	59.4 (3.0)	58.7 (3.0)	58.3 (3.1)	57.9 (3.3)
Group 2	56.7 (2.5)	62.4 (2.5)	63.7 (2.6)	65.0 (1.8)
Group 3	59.9 (2.9)	56.1 (1.7)	54.1 (1.7)	53.3 (1.6)
Group 4	55.3 (4.2)	54.4 (3.9)	52.9 (3.6)	51.6 (3.5)
CI (litre min^{-1} m^{-2})				
Group 1	2.26 (0.13)	2.43 (0.15)	2.47 (0.16)	2.42 (0.17)
Group 2	2.31 (0.19)	2.65 (0.17)	2.65 (0.15)	2.64 (0.17)
Group 3	2.46 (0.18)	2.37 (0.15)	2.28 (0.11)	2.29 (0.12)
Group 4	2.38 (0.16)	2.29 (0.14)	2.30 (0.09)	2.17 (0.13)
CVP (mm Hg)				
Group 1	9.3 (1.9)	7.4 (1.1)	6.5 (0.8)	6.5 (0.8)
Group 2	6.5 (0.9)	4.5 (0.8)	4.3 (1.0)	4.1 (1.0)
Group 3	7.7 (1.0)	5.5 (1.4)	5.5 (1.6)	5.7 (1.7)
Group 4	7.2 (1.3)	5.1 (1.1)	5.1 (1.1)	5.3 (1.2)
PAP (mm Hg)				
Group 1	19.9 (2.1)	19.1 (1.7)	18.2 (1.7)	17.9 (1.7)
Group 2	17.2 (1.2)	16.0 (1.7)	16.2 (1.8)	15.4 (1.5)
Group 3	19.1 (1.5)	18.1 (1.6)	17.2 (1.6)	17.3 (1.4)
Group 4	19.1 (1.7)	17.3 (1.5)	16.4 (1.4)	16.7 (1.7)
PCWP (mm Hg)				
Group 1	11.8 (1.7)	10.9 (1.6)	9.7 (0.7)	9.7 (0.8)
Group 2	8.8 (1.0)	8.4 (1.5)	7.7 (1.4)	7.5 (1.1)
Group 3	11.2 (1.2)	9.3 (1.3)	9.7 (1.4)	9.6 (1.5)
Group 4	9.4 (1.1)	7.6 (1.1)	7.6 (1.0)	8.0 (1.2)

group 4) resulted in a small but statistically significant decrease in HR over time. However, comparisons between group 4 and the lower dose doxacurium group (group 1) revealed no significant difference in haemodynamic effects.

Figure 1 illustrates the actual changes from baseline values in MAP and HR over the 10-min period after administration of doxacurium, pancuronium or vecuronium. Mean changes in MAP after doxacurium were unrelated to the dose of doxacurium, were similar to those after vecuronium and were small (±2 mm Hg). Small mean decreases in mean HR were observed after doxacurium (1–4 beat min^{-1}), and more pronounced decreases after vecuronium (4–7 beat min^{-1}). Mean changes after pancuronium represented 5–6 mm Hg increases in MAP and 6–8 beat min^{-1} increases in HR.

In order to illustrate further the changes in MAP and HR after doxacurium, pancuronium or vecuronium, the maximum changes in MAP and in HR observed in each individual patient in the 10-min period after administration of the blocking drug, expressed as a percentage of the baseline value, were plotted graphically (fig. 2). Maximum changes in MAP and in HR did not necessarily occur at the same time. After doxacurium, although there is some degree of inter-patient variation, data points are generally clustered symmetrically around the origin, although a majority of patients in the high dose group demonstrated a reduction in HR. However, no patient receiving doxacurium experienced a >20% increase or decrease in MAP or HR. In contrast, data points for pancuronium are distributed generally in the upper right quadrant, indicating increases in both HR and MAP. Two patients receiving pancuronium had >20% increases in both MAP and HR, and in two others, HR alone increased by >20%. Inter-patient variation was also more pronounced in patients who received vecuronium; most had a reduction in HR, and one patient a >20% decrease in both HR and MAP (fig. 2).

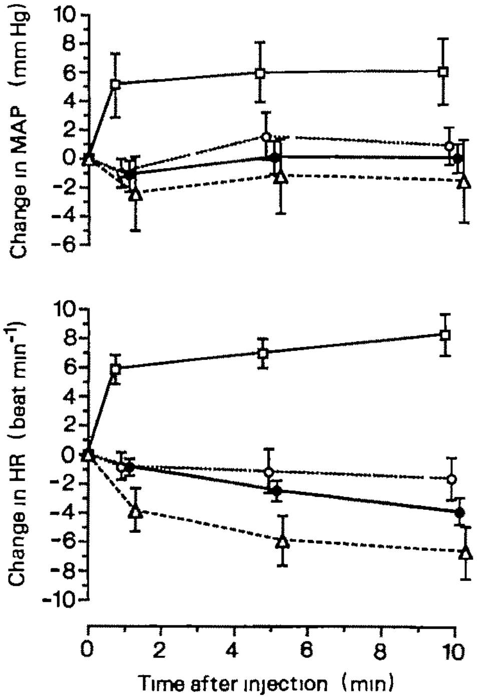
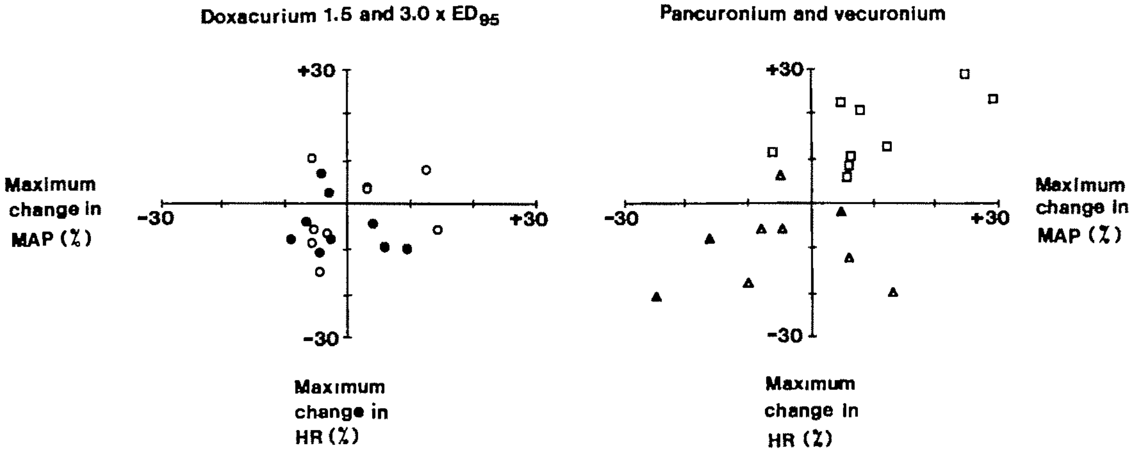


FIG. 1. Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration of doxacurium 0.037 mg kg^{-1} (○), doxacurium 0.075 mg kg^{-1} (●), pancuronium 0.09 mg kg^{-1} (□) or vecuronium 0.075 mg kg^{-1} (△).

DISCUSSION

The study was designed to minimize interacting influences such as medical status, medication, anaesthetic drugs and surgical manipulation. Dose of induction agent was titrated to the individual response of each patient and suxamethonium was used to facilitate rapid tracheal intubation. This technique has been used in previous studies investigating the haemodynamic effects of neuromuscular blocking drugs [5, 9]. We have not found any report of bradycardia at laryngoscopy in other similar studies, although of the first 10 patients investigated, seven developed clinically significant bradycardia requiring administration of atropine at laryngoscopy or intubation. This included two patients with sinus node arrest at laryngoscopy. We cannot explain why our patients behaved differently from those in other studies, but on reviewing our initial experience we decided to administer atropine at induction to the remaining 26 patients in the study. As the effect of


Doxacurium 1.5 and 3.0 x ED$_{95}$

Pancuronium and vecuronium

FIG. 2. Maximum % changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) observed at 1, 5 and 10 min after administration of doxacurium 0.037 mg kg^{-1} (○), doxacurium 0.075 mg kg^{-1} (●) (1.5 and 3.0 × ED$_{95}$ values, respectively), pancuronium 0.09 mg kg^{-1} (□) or vecuronium 0.075 mg kg^{-1} (△). Each point represents data from a single patient.

i.v. atropine on HR persists for 6 h or longer in unpremedicated awake healthy individuals [10], it seems likely that its administration may have influenced the haemodynamic changes observed after administration of neuromuscular blocking drug in this study. However, as the mean dose of atropine and the mean time interval between administration of atropine and non-depolarizing blocker were similar in all groups, the influence of atropine was probably also similar in all groups.

Doxacurium in doses of 0.037 mg kg^{-1} and 0.075 mg kg^{-1} was thought to represent approximate 1.5 and 3.0 × ED_{95} multiples, based upon an ED_{95} estimate for doxacurium of 0.025 mg kg^{-1} [11]. The doses of pancuronium and vecuronium selected for use were approximately equipotent to doxacurium 1.5 × ED_{95}, based on ED_{95} values estimated by single-dose methodology during opioid anaesthesia [12–14].

Our study has demonstrated that doxacurium was a cardio-stable neuromuscular blocking agent in patients with significant coronary artery disease when administered under the conditions described. This stability has been described by other workers both in healthy patients [6, 7] and in those with significant coronary arterial or valvular heart disease [9].

Several workers have reported increases in HR, MAP and CO after administration of pancuronium [4, 5, 15, 16] and our results are in general agreement. It is worth noting that the prior administration of atropine in the present study did not prevent an increase in HR after pancuronium, contrary to the suggestion of Kelman and Kennedy [15]. However, two of the nine patients in the pancuronium group did not receive atropine and in both patients a >20% increase in HR was observed. Atropine may, therefore, attenuate pancuronium-induced increases in HR, presumably by modification of the inhibition by pancuronium of vagal muscarinic receptors, but was unable to prevent these increases under the conditions of the present study.

Vecuronium has been found to be relatively free from direct haemodynamic side effects [4, 16]. However, intraoperative bradycardia after vecuronium has been described [17], and it is thought to result from lack of antagonism of vagotonic influences such as anaesthetic drugs and surgical manoeuvres. With the exception of fentanyl, administered at least 20 min before the study drug, these influences were absent during the period of study, yet a decrease in HR was observed after vecuronium and high-dose doxacurium. A significant reduction in HR (9.1%) following vecuronium during fentanyl anaesthesia in patients presenting for CABG surgery compared with a smaller reduction (3.8%) in control patients who did not receive a neuromuscular blocking agent led Salmenpera and colleagues [5] to suggest that other factors, such as onset of neuromuscular block *per se*, may have been responsible for the reduction in HR after vecuronium. This mechanism may account for the differences in HR changes observed in patients receiving vecuronium and doxacurium in the present study, as the onset time of a 1.5 × ED_{95} dose of doxacurium is longer than that of vecuronium 0.075 mg kg^{-1} and doxacurium 0.075 mg kg^{-1} [6, 18].

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USE OF POST-TETANIC COUNT IN ASSESSMENT OF A REPETITIVE VECURONIUM-INDUCED NEUROMUSCULAR BLOCK†

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SUMMARY

In order to evaluate the use of the post-tetanic count (PTC) method during repetitive administration of vecuronium, we studied 20 patients allocated randomly to one of two groups: 10 patients received droperidol–fentanyl anaesthesia (control group); 10 other patients were given droperidol–fentanyl anaesthesia modified subsequently by addition of 0.5% isoflurane (isoflurane group). Before tracheal intubation, a bolus dose of vecuronium 0.08 mg kg^{-1} was given i.v. followed by repeated doses of 0.03 mg kg^{-1}. The twitch response of adductor pollicis was recorded after supramaximal stimulation of the ulnar nerve at the wrist using a Myograph 2000 neuromuscular transmission analyser. In the control group, a close correlation was found between PTC and time to first reaction to train-of-four (TOF) nerve stimulation. This relationship was unchanged when comparing the bolus dose and each of eight consecutive maintenance doses. Further, the degree and the duration of intense block were unchanged after each of the eight maintenance doses. In the isoflurane group, the relationship between PTC and time to first reaction to TOF stimulation remained unchanged after addition of isoflurane. However, isoflurane caused a significant prolongation of the duration of intense block and a corresponding lower PTC in all patients. We conclude that PTC is a reliable method to evaluate intense neuromuscular block caused by vecuronium, even after repetitive administration of the drug and in combination with 0.5% isoflurane.

KEY WORDS

Monitoring neuromuscular function. Neuromuscular relaxants: vecuronium.

During intense non-depolarizing neuromuscular block there is no response to single twitch or train-of-four (TOF) nerve stimulation. After a single bolus injection of atracurium, vecuronium or pancuronium this "period of no response" may be quantified by counting the number of post-tetanic twitches: the post-tetanic count (PTC) [1–3]. The time to appearance of the first reaction to TOF nerve stimulation is related closely to the number of twitches detectable. The duration of the period of no response may be predicted therefore, by using PTC [3].

Information is lacking on the use of PTC following repeated injections of non-depolarizing neuromuscular blocking drugs. Also, it is not clear how the addition of an inhalation anaesthetic agent to opioid-based anaesthesia affects this relationship and the degree of block during the period of no response.

The aims of this study were to elucidate the temporal relationship between PTC and the first reaction to TOF stimulation after repeated injections of vecuronium during opioid-based anaesthesia, to determine if duration and intensity of the neuromuscular block are changed after repetitive administration of the same dose of vecuronium, and if either of these is influenced by addition of 0.5% isoflurane.

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PATIENTS AND METHODS

We studied 20 patients (ASA physical status I) undergoing reconstructive middle ear surgery or translabyrinthal operations on neuroma of the acoustic nerve. Informed consent was obtained from all patients and the study was approved by the Ethics Committee of Linköping University Hospital. The patients were allocated randomly to receive either opioid-based anaesthesia without addition of isoflurane (control group, $n = 10$) or opioid-based anaesthesia modified subsequently by addition of 0.5% isoflurane (end-tidal concentration) (isoflurane group, $n = 10$).

All patients were premedicated with oxicodone 0.1 mg kg^{-1} and hyoscine 0.005 mg kg^{-1} i.m. 60–90 min before surgery. Anaesthesia was induced with droperidol 0.20–0.35 mg kg^{-1} and fentanyl 0.004–0.007 mg kg^{-1} i.v. Tracheal intubation was performed after administration of a bolus dose of vecuronium of 0.08 mg kg^{-1} i.v. During surgery, repeated injections of vecuronium of 0.03 mg kg^{-1} were given when the TOF ratio reached 0.25. The lungs were ventilated with 65% nitrous oxide in oxygen using a Servo Ventilator 900 B (Siemens-Elema, Sweden). Additional increments of fentanyl were administered as required to maintain stable anaesthesia. The end-tidal concentration of carbon dioxide and inspired fraction of oxygen ($F\text{I}_{\text{O}_2}$) were monitored using a Normocap capnograph (Datex, Finland). Ventilation was adjusted to maintain end-tidal carbon dioxide at approximately 4 kPa and $F\text{I}_{\text{O}_2}$ 0.35. During surgery, a balanced glucose–saline solution (Rehydrex, Pharmacia, Sweden) was given i.v. at a rate of 5 ml kg^{-1} h^{-1}.

In the isoflurane group all patients received four maintenance doses of vecuronium 0.03 mg kg^{-1} before the anaesthetic procedure was modified by addition of isoflurane. When the fifth maintenance dose of vecuronium was given, isoflurane was added from a Servo vaporizer (Siemens-Elema, Sweden) adjusted to deliver an end-tidal isoflurane concentration of 0.5% as monitored by a Normac gas monitor (Datex, Finland). Steady-state end-tidal isoflurane concentration was obtained within 10–15 min. In all patients supramaximal stimulation (square wave impulses, 200 ms duration) was delivered to the ulnar nerve at the wrist via skin electrodes using a Myotest nerve stimulator (Biometer, Denmark). TOF nerve stimulation (2 Hz for 2 s every 12 s) was applied with a continuous preload of 0.30 kg on the thumb. The evoked twitch response of adductor pollicis was monitored and recorded using a Myograph 2000 neuromuscular transmission analyser (Biometer, Denmark) [4].

The post-tetanic count was measured as follows: every 6 min, after administration of the bolus dose for tracheal intubation and after administration of each maintenance dose, tetanic nerve stimulation (50 Hz for 5 s) was applied followed by a 3-s pause. On each occasion the tetanic stimulation was preceded by a 1-min period of 1 Hz single twitch stimulation which was continued after the 3-s pause. The degree of neuromuscular block was estimated by observing the number of post-tetanic twitches. When there was no response to the 1-Hz stimulation or the observed post-tetanic response had faded to zero, TOF mode of stimulation was reinstituted until 1 min before the next tetanic stimulation. The cycle was repeated until the first reaction to TOF stimulation was detected [1]. All patients received at least six maintenance doses of vecuronium and the mean duration of anaesthesia was 6.4 h (range 3.7–14.5 h).

Skin temperature over adductor pollicis and oesophageal temperature were measured continuously (Electric thermometer, Ellab Ltd, Denmark). ECG, heart rate and systolic arterial pressure were monitored also.

Statistics

Results are presented as mean (SD). The paired and unpaired Student's t test were used when comparing results for the two groups. $P < 0.05$ was considered statistically significant. Analysis of linear regression was used and the relationships obtained were tested for similarity using analysis of variance.

RESULTS

Control group

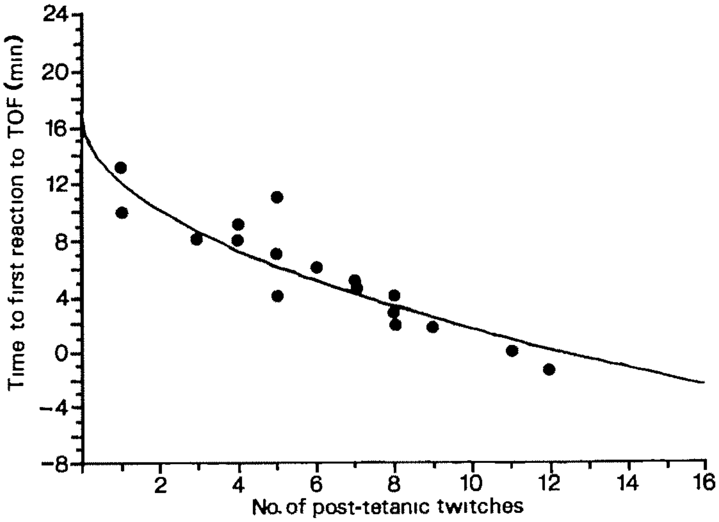
Seven men and three women were studied. Mean age was 39 (13) yr (range 21–58 yr) and mean body weight was 75 (12) kg.

After the bolus dose for tracheal intubation and for each of eight maintenance doses, a close linear relationship was found between time to first reaction to TOF nerve stimulation and square root of PTC. As found previously [1] the relationship was described best by:

$$t = a + b\sqrt{\text{PTC}}$$

TABLE I. *Regression variables for the bolus dose and eight consecutive maintenance doses of vecuronium (0.03 mg kg^{-1} i.v.) in the control group* (n = *10 except* †n = *7*)

		Maintenance dose							
	Bolus	1st	2nd	3rd	4th	5th	6th	7th†	8th†
a (intercept)	16.4	17.1	18.9	17.5	16.3	18.6	18.6	17.1	17.2
b (slope)	−4.7	−5.0	−5.6	−5.2	−4.6	−5.3	−5.3	−6.3	−4.8
Residual SD	2.45	1.81	1.53	2.07	1.79	2.09	1.91	2.25	1.77
Correlation coefficient	−0.85	−0.90	−0.92	−0.87	−0.88	−0.88	−0.90	−0.86	−0.90
P	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001



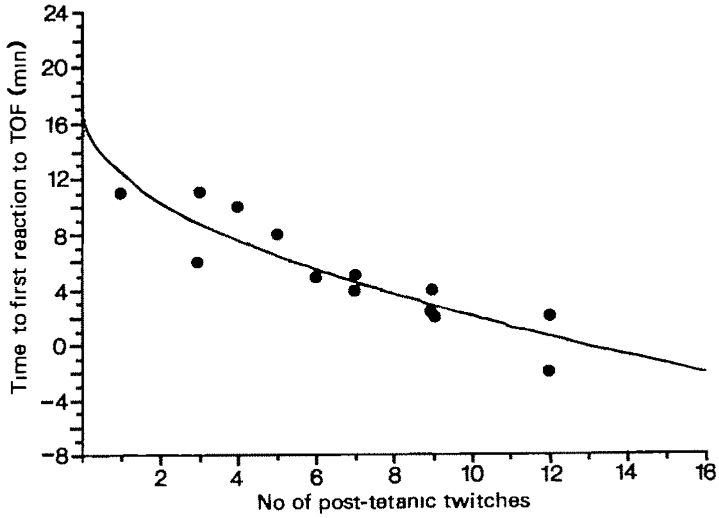


FIG. 1. Relationship between post-tetanic count (PTC) and time to onset of response to TOF stimulation following the first (upper curve) and the eighth (lower curve) maintenance dose of vecuronium 0.03 mg kg^{-1} i.v. during opioid-based anaesthesia. Individual data points and predicted mean curve.

TABLE II. *Mean* (SD) *duration of period of no response and number of post-tetanic twitches (PTC) in 10 patients during opioid-based anaesthesia. Measurements of PTC were made 4 and 10 min after injection of the second, fourth, sixth and eighth maintenance doses* ($0.03\ mg\ kg^{-1}$ *i.v.*) *of vecuronium.* †n = 7

	Maintenance dose			
	2nd	4th	6th	8th†
Duration of period of no response (min)	11.6 (3.0)	11.8 (2.7)	11.5 (3.2)	11.4 (3.8)
Number of post-tetanic twitches				
After 4 min	4.7 (2.7)	4.3 (2.5)	4.9 (2.7)	4.8 (2.8)
After 10 min	8.6 (2.7)	8.6 (2.5)	9.3 (3.5)	9.2 (3.7)

where t = the time interval between a given PTC and the first detectable response to TOF stimulation; a = a constant (intercept) and b = the regression coefficient (slope) of this linear relationship.

The regression coefficients were tested for similarity. There was no significant difference for slope (b coefficient), or intercept (a coefficient) when comparing curves obtained following the bolus dose and each of the eight consecutive maintenance doses. The regression parameters for the bolus dose and each of the eight maintenance doses are presented in table I. In figure 1 the curve including individual data points for the first and the eighth maintenance dose is presented.

All patients had a near constant degree of neuromuscular block and an unchanged duration of period of no response following the eight maintenance doses of vecuronium (table II). However, both variables showed considerable variation between patients.

Isoflurane group

Six men and four women were studied. Mean age was 45 (14) yr (range 20–62 yr) and mean body weight 75 (16) kg. A close linear relationship was found between time to first reaction to TOF nerve stimulation and square root of PTC. When comparing the regression coefficients before addition of isoflurane (the first, second, third and fourth maintenance dose) with the relationship obtained after addition of isoflurane (the fifth, sixth, seventh and eighth maintenance dose) there was no significant difference. In figure 2 the curve for the four initial maintenance doses (before addition of isoflurane) and the curve for the fifth to eighth doses (after addition of isoflurane) including individual data points, are presented. Regression parameters for each of the eight maintenance doses are presented in table III. The mean duration of period of no response was approximately 10 min before isoflurane, showing a significant increase to approximately 14 min after addition of isoflurane ($P < 0.01$) (table IV). The prolongation of duration of the period of no response varied considerably between each patient (table IV). Furthermore, the depth of neuromuscular block was increased by addition of isoflurane, as indicated by a significant reduction in number of post-tetanic twitches when comparing measurements before and after addition of isoflurane, respectively ($P < 0.01$) (table IV).

Statistical analysis of the relationship between PTC and the time to first reaction to TOF nerve stimulation showed that the correlation was the same during opioid-based anaesthesia and after addition of 0.5% isoflurane. The data from the control and the isoflurane group were therefore pooled. The mean curve obtained, including the 95% prediction interval, is presented in figure 3. From this graph, the expected time of onset of TOF response may be predicted from the PTC during isoflurane or opioid-based anaesthesia, independently of the number of doses of vecuronium given.

Skin temperature over adductor pollicis and oesophageal temperature remained unchanged in both groups. Systolic arterial pressure was stable throughout anaesthesia (both groups) and showed only minor variation following addition of isoflurane (isoflurane group).

DISCUSSION

Control group

The relationship between PTC and the time to the first reaction to TOF nerve stimulation following a single bolus dose of vecuronium 0.08 mg kg^{-1} i.v. has been described previously [3]. In this investigation we have demonstrated that this

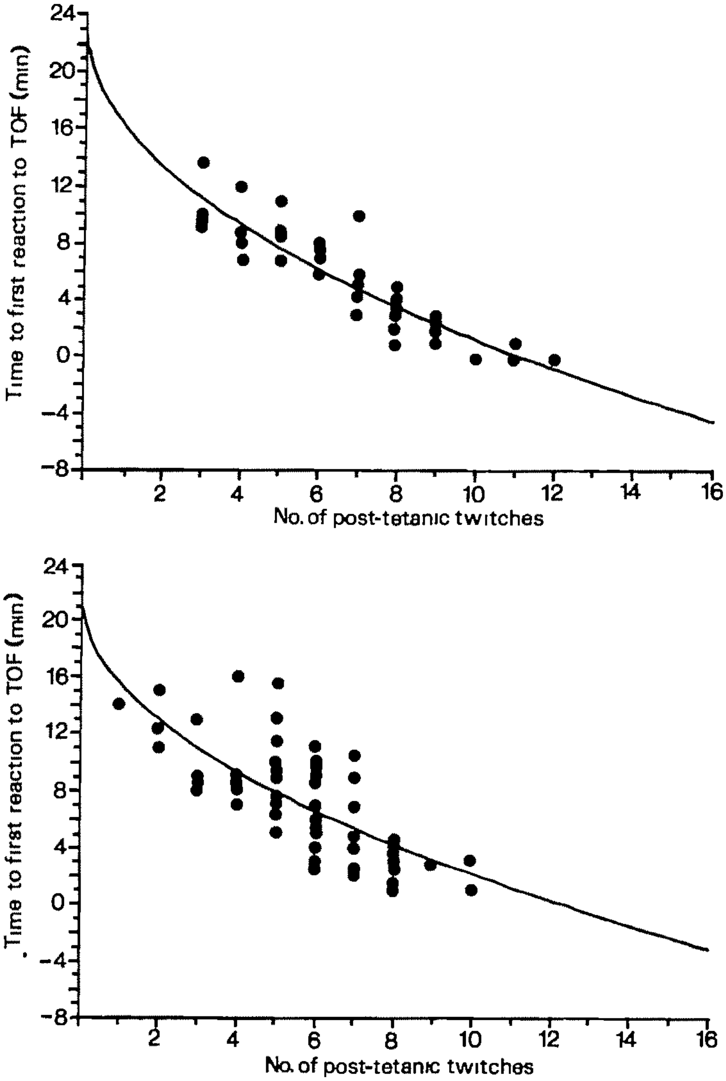


FIG. 2. Relationship between post-tetanic count (PTC) and time to first reaction to TOF stimulation during repetitive vecuronium-induced neuromuscular block (0.03 mg kg^{-1} i.v.) before addition of 0.5% isoflurane (upper curve) and after addition of 0.5% (steady state end-tidal concentration) isoflurane (lower curve). Individual data points and predicted mean curve.

TABLE III. *Regression variables for eight consecutive maintenance doses of vecuronium 0.03 mg kg^{-1} i.v. in the isoflurane group* (n = *10 except* †n = *9*)

	Maintenance dose							
	1st	2nd	3rd	4th	5th	6th	7th	8th†
a (intercept)	22.2	21 7	24.3	24.3	25.7	24.0	22.8	21.5
b (slope)	-6.8	−6.4	−7.3	−7.2	−7.6	−7.4	−5.3	−6.0
Residual SD	1.15	1.41	1.30	1.63	2.14	2.80	2.98	3.0
Correlation coefficient	−0.94	−0.92	−0.92	−0.90	−0.80	−0.76	−0.70	−0.70
P	0.0001	0.0001	0 0001	0.0001	0.0001	0.0003	0.0022	0.0022

TABLE IV. *Mean* (SD) *duration of period of no response and number of post-tetanic twitches (PTC) in 10 patients receiving opioid-based anaesthesia modified subsequently by addition of 0.5% (end-tidal concentration) isoflurane. Measurements of PTC 4 and 10 min after injection of the second and fourth maintenance doses (before addition of isoflurane) and the sixth and eighth maintenance doses (after addition of 0.5% isoflurane) of vecuronium 0.03 mg kg^{-1} i.v. are presented. When comparing the duration of period of no response and the number of post-tetanic twitches for the maintenance doses before addition of isoflurane (second and fourth) with those given after addition of 0.5% isoflurane (sixth and eighth), the changes are significant* (**$P < 0.01$). †n = 9

	Maintenance dose			
	2nd	4th	6th	8th†
Duration of period of no response (min)	10.1 (3.1)	11.1 (2.8)	14.0 (4.0)**	14.0 (3.5)**
Number of post-tetanic twitches				
After 4 min	6.2 (2.3)	6.1 (2.3)	4.4 (1.6)**	4.2 (1.7)**
After 10 min	9.1 (2.2)	8.2 (1.2)	6.7 (1.2)**	6.0 (1.7)**

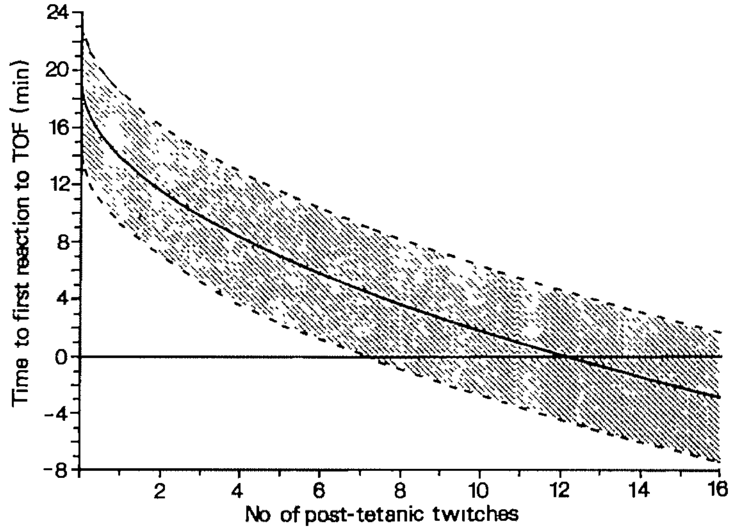


FIG. 3. Relationship between PTC and time to first reaction to TOF stimulation during repetitive vecuronium-induced neuromuscular block in the 20 patients investigated. In the regression analysis are included all data obtained after the eight maintenance doses in both groups. Predicted mean curve with 95% prediction interval.

correlation holds true for at least up to eight maintenance doses of vecuronium of 0.03 mg kg^{-1}. This is in accordance with a previous report [5], where we found vecuronium had a stable duration of action and recovery time following repetitive administration of 0.02 mg kg^{-1} during long-lasting opioid-based anaesthetic procedures. In addition, we found that the intensity of neuromuscular block during the period of no response was unchanged following repetitive injections of vecuronium. These findings confirm the previously reported lack of cumulative properties of vecuronium when administered in repeated doses of 0.03 mg kg^{-1} i.v.

Isoflurane group

Before the addition of isoflurane, that is following the first to fourth maintenance doses, each patient had the same degree of neuromuscular block following each injection of blocker as indicated by an unchanged number of post-tetanic twitches and duration of period of no response, respectively. Following administration of the fifth maintenance dose of vecuronium, isoflurane was added in an end-tidal concentration of 0.5%. After steady-state end-tidal concentration of isoflurane was obtained (from the sixth maintenance dose of vecuronium onwards), the measurements showed a significant reduction in number of post-tetanic twitches and a corresponding increase in duration of the period of no response. Thus, as expected, the addition of isoflurane potentiated the neuromuscular blocking effect of vecuronium. However, the correlation between PTC and time to the first appearance of response to TOF stimulation remained unchanged. Hence, the recovery time from a certain level of intense block until appearance of the first response to TOF stimulation was unaffected by the addition of 0.5% isoflurane. Our findings suggest, therefore, that isoflurane potentiated intense vecuronium-induced block mainly by a change in pharmacodynamic properties rather than alteration in pharmacokinetics. This is in accordance with recent findings by Cannon and co-workers [6], who demonstrated that the plasma clearance of vecuronium during continuous infusion was the same in patients receiving balanced i.v. anaesthesia and those receiving 1.2% isoflurane anaesthesia.

In both groups neuromuscular transmission was investigated during standardized conditions (stable peripheral circulation, body and hand skin temperature, and constant end-tidal $P\text{CO}_2$, $F\text{I}_{\text{O}_2}$ and isoflurane concentration). Patients did not lose blood and no drugs were administered that might affect neuromuscular transmission. Following administration of isoflurane, systolic arterial pressure showed only minor variations and the peripheral hand skin temperature remained unchanged.

We conclude that PTC is a reliable method of evaluating intense neuromuscular block caused by vecuronium, even after repetitive administration of the drug and in combination with isoflurane in an end-tidal concentration of 0.5%.

ACKNOWLEDGEMENT

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EFFECT OF SURFACE ELECTRODE POSITION ON THE COMPOUND ACTION POTENTIAL EVOKED BY ULNAR NERVE STIMULATION DURING ISOFLURANE ANAESTHESIA

I. KALLI

SUMMARY

The effect of surface electrode positioning on the evoked compound action potential was studied during isoflurane anaesthesia without neuromuscular block. In 20 ASA I–II patients (age 36–50 yr), the response after supramaximal ulnar nerve stimulation was analysed with a neuromuscular relaxation monitor (Relaxograph, Datex) and with a memory recorder. Seven pairs of surface recording electrodes were compared: (1) adductor pollicis muscle vs *second finger; (2) adductor pollicis m.* vs *first finger; (3) first dorsal interosseus m.* vs *second finger; (4) abductor digiti minimi m.* vs *fifth finger; (5) adductor pollicis m.* vs *second dorsal metacarpal; (6) abductor digiti minimi m.* vs *fourth dorsal metacarpal; (7) thenar* vs *hypothenar. Steady biphasic response was recorded with electrode pairs 1–4. Marked variation and low amplitude existed at pairs 5–7. Peak-to-peak amplitude at pair 3 was the greatest (12.5 (SD 3.7) mV) compared with pair 4 (9.4 (SD 2.0) mV) and pair 1 (8.5 (SD 2.0) mV). A close correlation between the amplitudes and integrated areas was found. The first dorsal interosseus muscle response was optimal and the electrodes were simple to fix; this site may be recommended for clinical monitoring.*

KEY WORDS

Measurement techniques: neuromuscular junction, electrode position. Neuromuscular transmission · action potentials

Techniques for assessment of neuromuscular block have been developed to optimize drug administration and reduce the risk of residual curarization after operation [1, 2]. In clinical anaesthesia, the evoked compound action potential (ECAP) response of the hand muscles [3–6] may be used to monitor neuromuscular block.

The characteristics of the ECAP evoked by ulnar nerve stimulation depend on the positioning of both the stimulus and the recording electrodes [7–8]. In routine clinical practice, there is not time for fine-tuning of electrodes, therefore those recording sites which give the best response should be used. The present study was designed to analyse the effect of recording electrode position on ECAP during standardized isoflurane anaesthesia without neuromuscular block.

PATIENTS AND METHODS

After the approval of the Ethics Committee of the Surgical Hospital and with informed consent, 20 female patients (ASA I–II) with no disease and receiving no medication affecting the neuromuscular junction were studied. Patients were aged 36–50 yr and of normal body weight (50–88 kg) and height (153–176 cm). Eighteen required elective surgery for breast cancer, one for varicose veins of the lower extremities and one thyroidectomy.

Premedication was oral diazepam 0.15 mg kg^{-1} combined with i.m. oxycodone 0.14 mg kg^{-1} 1 h before surgery. Continuous monitoring of ECG, oscillometric arterial pressure, oxygen saturation and peripheral temperature from the proximal phalanx of the third finger on the recorded side

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was commenced before operation. Cooling of that hand was prevented with a warming blanket. During preoxygenation, glycopyrrolate 0.2 mg and fentanyl 0.1 mg were administered i.v. and sleep was induced with thiopentone 3–5 mg kg^{-1} i.v. Tracheal intubation was facilitated with suxamethonium 1 mg kg^{-1} i.v. Thereafter, inspiratory and expiratory concentrations of oxygen, carbon dioxide, nitrous oxide and isoflurane were measured continuously with an infra-red analyser (Capnomac, Datex). Ventilation of the lungs was controlled using 66 % nitrous oxide in oxygen and adjusted to achieve normocapnia. Administration of 2–4 % isoflurane was started after tracheal intubation, and adjusted to achieve an end-tidal concentration of 0.5 % in 5 min. Thereafter, end-tidal concentration was kept constant at 0.5 % throughout the study, by increasing or decreasing the vaporizer setting as required. Increments of fentanyl were given when indicated. After induction of anaesthesia, 30 min was allowed for stabilization, during which time Ringer's lactate 500–750 ml was administered to ensure optimal peripheral circulation. Recovery from suxamethonium block was assessed with a neuromuscular relaxation monitor (Relaxograph NMT-100 rev.01, software 3.0, Datex, Finland) [6]. No other neuromuscular blocking drug was used during the study. ECAP was recorded within 30–60 min from the induction of anaesthesia.

The recorded hand was selected at random; in the breast cancer operations, however, the hand contralateral to the operated side was always used. The arm was supported in a splint and the skin cleaned with alcohol. The disposable surface electrodes (Datex 57268, pre-gelled, diameter 12.5 mm) were attached after induction of sleep to allow them to warm before the study period. Eight recording electrodes were attached to the hand to form seven pairs for measurements (fig. 1).

Two stimulating electrodes were positioned on the ulnar nerve at the wrist. The polarity of the distal stimulation electrode was always negative [9], and its distance from the hypothenar motor point was kept constant (8 cm). A grounding electrode was positioned between the stimulus and recording electrodes in order to minimize stimulus artefact [10]. The position of the stimulating electrodes on the ulnar nerve was selected according to the best response with the nerve locator (Datex 874763) of the neuromuscular relaxation monitor.

The neuromuscular relaxation monitor was recalibrated every time a new electrode pair was selected for the recordings. Supramaximal response was determined utilizing automatic cali-

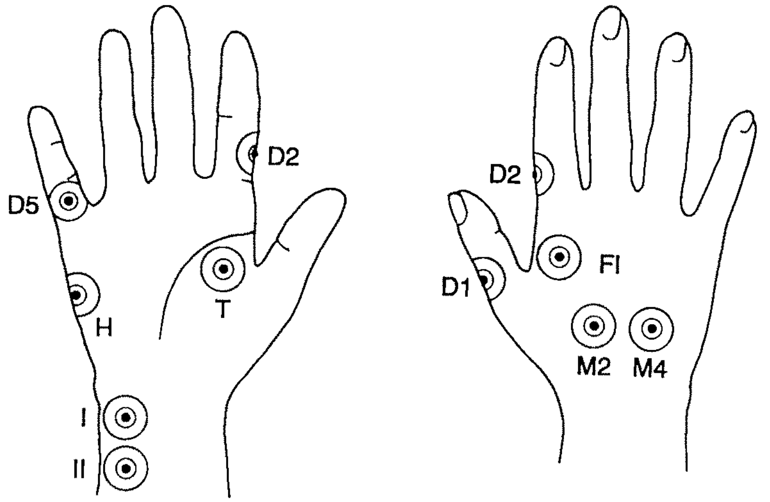

FIG. 1. Stimulus and recording electrode positions. Negative (I) and positive (II) stimulating electrodes were attached on the ulnar nerve at the wrist. Eight recording electrodes were attached on the hand. 1–3: On muscle motor points of adductor pollicis (thenar) (T), abductor digiti minimi (hypothenar) (H) and first dorsal interosseus (FI); 4–5: on the second (M2) and forth (M4) dorsal metacarpal interspaces; 6–8: on the proximal phalanx of the first (D1) second (D2) and fifth (D5) finger. For evoked compound muscle action potential recordings, seven active *vs* indifferent electrode pairs were formed: T *vs* D2, T *vs D1, T vs* M2, FI *vs* D2, H *vs* D5, H *vs* M4 and T *vs H*. Thus the recording electrode positions compared are TD2, TD1, TM2, FID2, HD5, HM4 and TH.

bration which gradually increased the stimulus current. When the supramaximal response was reached, the delivered current was increased automatically by 10%; this was the stimulus used in the recordings. The maximum stimulus current of the device was limited to 70 mA. Using a single supramaximal square wave 0.1 ms stimulus impulse, three subsequent ECAP responses were recorded at each electrode pair. The median of the responses was selected. The minimum delay between two adjacent stimuli was 20 s. Recordings were started randomly from the thenar or hypothenar sides of the hand. After all seven pairs of electrodes had been measured, a post-study control was recorded from the same electrode pair which had been first used.

Stimulus response was pre-amplified and band-pass filtered from 60 to 330 Hz in the neuromuscular relaxation monitor, and transferred through its analogue output to a memory recorder (Hioki 8810 Memory HiCorder, Hioki E. E. Co., Japan). Memory recording was started with a trigger pulse provided simultaneously with the nerve stimulus. The same relaxation monitor was used in all cases; its internal amplification was verified with a signal generator.

The baseline for measurements was defined as the value before the trigger pulse. Onset latency (DL) was measured from the end of the trigger pulse to the first ECAP deflection from the baseline. In the case of biphasic responses, durations of negative (DZ′) and positive (DZZ′) half-waves were measured between the points where the curve crossed the baseline (fig. 2). Peak-to-peak amplitude and amplitude of the negative half-wave were measured also. The area under the curve from 4 to 14 ms was integrated manually.

Analysis of variance with Welch modification in case of unequal variances, and *t* test with Bonferroni correction were used for comparison between the recording electrode pairs. Student's *t* test for paired data was used when pre-study and post-study controls were compared. The area and amplitude of the response curve were compared with linear regression analysis. $P < 0.05$ was regarded as statistically significant.

RESULTS

The duration of the recording period was 26.8 (SD 7.5) min. A supramaximal response was obtained at each recorded position ($n = 140$). In 69% of the recorded responses the stimulus current ranged from 45 to 57 mA, but in 31% of responses a current from 60 to 70 mA was required. Skin temperature on the recorded hand was in the range 31.8–34.7 °C. There were no significant differences between the 13 paired pre-study and post-study control recordings, between the right and left hand recordings, or between the series recordings started from the thenar or hypothenar electrodes. The muscle action potentials were clearly biphasic in 97% of the recordings at TD1, TD2, FID2 and HD5. The number and amplitude of the positive and negative waves varied considerably at TM2, HM4 and TH, which were biphasic in only 30% of the recordings (fig. 2).

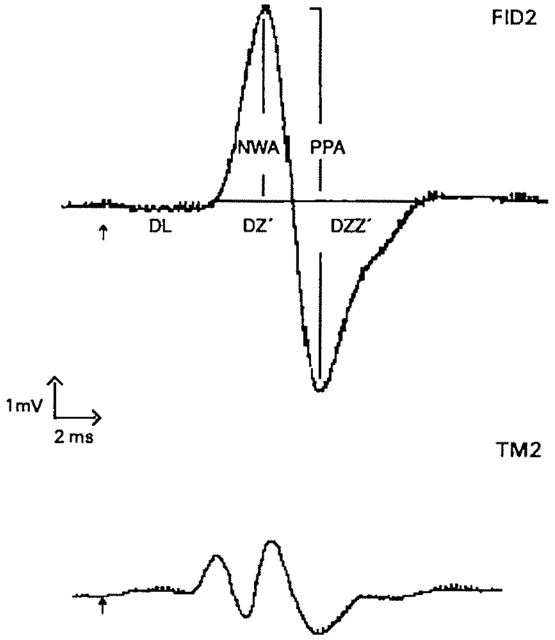

FIG. 2. Typical biphasic evoked compound action potential recorded from the first dorsal interosseus muscle (FID2). Onset latency (DL) was measured from the nerve stimulus (arrow). The durations of the negative (DZ′) and positive (DZZ′) half-waves are shown, in addition to peak-to-peak amplitude (PPA) and the amplitude (NWA) of the negative half-wave. A multi-phasic response (TM2) may result if both active and indifferent recording electrodes are placed on electrically active muscles.

Onset latencies on the thenar side of the hand were longer than on the hypothenar and metacarpal sites. The interosseus muscle onset latency (4.8 (0.4) ms) was the longest ($P < 0.001$ *vs* other electrode pairs except TD2). The shortest onset latency (4.0 (0.1) ms) was measured at electrode position HD5 ($P < 0.01$ *vs* FID2, TD2 and TD1).

TABLE I. *Evoked compound action potential latencies and durations* (n = *20*). *Responses at HM4, TM2 and TH were multiphasic, and half-wave durations are not shown.* *P < *0.05;* **P < *0.01;* ***P < *0.001*

	Onset latency (ms)	Negative half-wave duration (ms)	Positive half-wave duration (ms)
Electrode position			
HD5	4.0 (0.1)	4.1 (0.8)	5.6 (0.9)
TD2	4.5 (0.3)	3.8 (0.7)	6.0 (1.3)
TD1	4.2 (0.2)	3.6 (1.0)	6.8 (2.2)
FID2	4.8 (0.4)	2.7 (0.8)	6.8 (1.1)
HM4	4.0 (0.1)	—	—
TM2	4.1 (0.2)	—	—
TH	4.1 (0.2)	—	—
Significant differences between recording electrode positions			
Onset latency		**TD2 *vs* HD5, HM4, TM2, TH **TD1 *vs* HD5, HM4 ***FID2 *vs* all except TD2	
Negative half-wave duration		**FID2 *vs* HD5, TD2	
Positive half-wave duration		*FID2 *vs* HD5	

TABLE II. *Evoked compound action potential amplitudes and integrated areas* (n = *20*). *P < *0.05;* **P < *0.01*

	Peak-to -peak amplitude (mV)	Negative half-wave amplitude (mV)	Integrated area (mV·ms)
Electrode position			
HD5	9.4 (2.0)	4.7 (1.0)	52.2 (9.8)
TD2	8.5 (2.0)	4.5 (1.2)	39.5 (10.2)
TD1	6.2 (2.0)	3.6 (1.2)	31.2 (7.9)
FID2	12.5 (3.7)	7.0 (2.1)	56.7 (18.0)
HM4	6.1 (2.7)	3.3 (1.8)	24.7 (10.7)
TM2	6.4 (2.0)	3.5 (1.3)	25.8 (9.5)
TH	5.1 (2.3)	2.4 (1.0)	22.1 (10.4)
Significant amplitude differences between recording electrode positions			
Peak-to-peak amplitude		**HD5 *vs* TD1, TM2, HM4, TH *TD2 *vs* TD1, TH **FID2 *vs* TD1, TM2, HM4, TH	
Negative half-wave amplitude		**FID2 *vs* all other pairs **TH *vs* HD5, TD2	

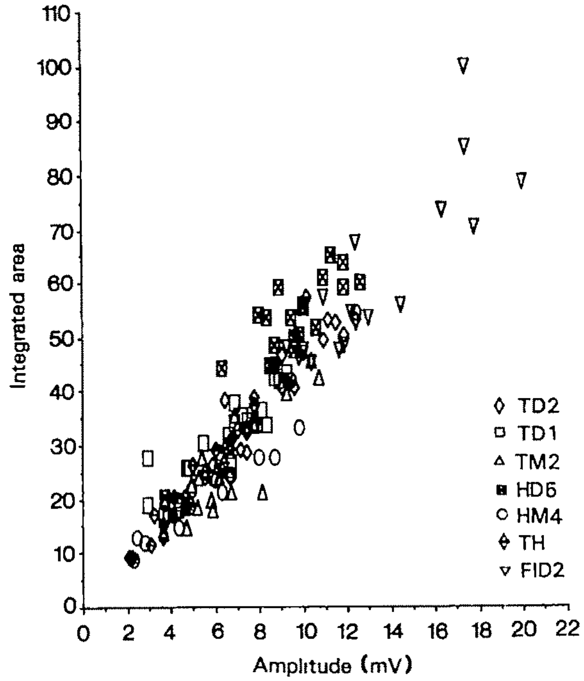

FIG. 3. Peak-to-peak amplitudes and integrated areas of the evoked compound action potential response curves ($n = 140$). A close correlation ($r = 0.9$, $P < 0.001$) exists.

Comparison between the half-wave durations was possible only with the biphasic responses. The first dorsal interosseus response negative wave duration (2.7 (0.8) ms) was significantly shorter ($P < 0.01$) compared with TD2 and HD5. No clinically significant differences were found between the positive wave durations. Latencies and durations are shown in table I. Peak-to-peak amplitude at the first dorsal interosseus muscle was the greatest (12.5 (3.7) mV), and differed significantly from TD1, TM2, HM4 and TH ($P < 0.01$). The negative half-wave amplitudes differed accordingly; first dorsal interosseus amplitude was the greatest (7.0 (2.1) mV) compared with others ($P < 0.01$). Amplitudes are shown in table II.

Peak-to-peak amplitude and integrated area were compared using linear regression analysis (fig. 3). At all seven recording sites, a significant correlation existed ($r = 0.9$, $P < 0.001$). The absolute values of the integrated area are included in table II.

DISCUSSION

The evoked compound action potential response of the hand muscles may be used conveniently for monitoring neuromuscular block. Technically, the method is relatively easy [11], using a supramaximal stimulus applied to the ulnar nerve [1–6]. To obtain the best response, the recording sites should be selected carefully. In this study, seven recording electrode positions were compared. The best response was obtained at the first dorsal interosseus muscle, which may be recommended, therefore, for clinical use. Although the second best site was the adductor pollicis muscle, its response was influenced by the positioning of the indifferent recording electrode.

Supramaximal stimulus response was obtained in all recordings. However, in 31% of measurements, a stimulus current of 60–70 mA was required, which is near or equal to the maximum output of the neuromuscular relaxation monitor (70 mA). This finding emphasizes the importance of correct electrode positioning.

Disposable surface electrodes are convenient, but their properties may affect the response [12]. Therefore, similar electrodes were used in all recordings of this study and a relaxation monitor nerve locator was used to define the correct site of stimulating electrodes on the ulnar nerve at the wrist. Misplaced electrodes may interfere with the responses by stimulating the underlying muscles or the median nerve.

Inhalation agents may affect nerve conduction and the neuromuscular junction [13]. To minimize such influences on the results, a period of stabilization was permitted before the responses were recorded in random order. Additionally, paired pre-study and post-study responses were recorded for comparison. There was a 30-min delay between paired control responses, but no statistical difference was found. Evidently, the slow baseline drift [14], which may take place during inhalation anaesthesia, had no effect on these results.

On the other hand, cooling may affect the nerve conduction velocity and recorded response [10, 15, 16]. In the present study, the finger skin temperature of the recorded hand was maintained at 32 °C or more. The effect of skin temperature on the response remains inconclusive.

Onset latencies in this study ranged from 4.0 to 4.8 ms, with no signs of stimulus artefact interference. Onset latency is affected most often by the length of the nerve conduction pathway. Thus it is understandable that the greatest latencies were measured at the interosseus and adductor pollicis motor points, and the smallest at the hypothenar site. Excessive variability of the response curves at TM2, HM4 and TH is in accordance with the previous findings in paediatric patients [8].

In the present study, biphasic muscle action potentials at TD1, TD2, FID2 and HD5, allowed comparison between the negative and positive half-waves. The positive half-wave curve may be affected by the time constant of the pre-amplifier band-pass filter. No clinically significant differences were found and the tail of the curve was always recorded completely. Negative half-wave duration was significantly shorter at the interosseus muscle motor point: 2.7 ms compared with 3.6–4.1 ms at the other positions. On the other hand, the first dorsal interosseus amplitude was greatest; its negative half-wave was nearly 1.5 times that of the hypothenar or adductor pollicis muscles. Compared with the other positions, the negative half-wave at the interosseus muscle was of high fidelity, and with less dispersion of the response.

In an electromyographic study, Harper [7] compared the adductor pollicis and first dorsal interosseus muscles following atracurium and vecuronium. Monitoring was based on ECAP amplitude, but detailed analysis of electromyographic responses was not given. The pattern of neuromuscular block at both recorded sites was similar, and the interosseus recording was regarded as well suited for clinical monitoring.

Hypothenar muscle monitoring of relaxation may be misleading, although the quality of the evoked compound action potentials at the hypothenar muscles (HD5) was found to be satisfactory in this study. Previously, Katz [17] has shown that the magnitude of block at the hypothenar muscles differed from that of the adductor pollicis. Ali and DeCesare [18] compared evoked mechanical and electromyographic responses following atracurium. They found that the thenar and hypothenar integrated responses differed, the thenar being more sensitive than hypothenar.

In the present recordings, a close correlation was found between the integrated area and peak-to-peak amplitude of the evoked compound action potential, which is in accord with the work of Pugh, Kay and Healy [19]. The values on the Relaxograph relaxation monitor display are based on the integrated area, although the recorded curves in this study were integrated manually to achieve more objectivity.

Positioning of the recording electrodes is an important element in the assessment of neuromuscular block by electromyography. For successful monitoring it is essential to select optimal sites. This study suggests that the first dorsal interosseus muscle may be recommended as the optimal site. It lies on the dorsal side of the hand between the first and second metacarpals, where surface electrodes are simple to fix, maintain their position, and are seldom disturbed by hand movements.

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PREOPERATIVE PIROXICAM FOR POSTOPERATIVE ANALGESIA IN DENTAL SURGERY

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SUMMARY

Fifty patients were allocated randomly to receive placebo or piroxicam 40 mg, 2.5 h before surgical removal of lower third molars under general anaesthesia. A significantly greater number of patients in the piroxicam group did not require opioid analgesia after operation ($P < 0.05$). The piroxicam group also required fewer doses of paracetamol in the first 24 h after recovery from anaesthesia ($P < 0.05$), and the time from recovery to first postoperative analgesia was longer in those patients who had received piroxicam ($P < 0.05$). Piroxicam did not significantly prolong the duration of recovery from anaesthesia.

KEY WORDS

Anaesthesia: dental Analgesia: postoperative. Analgesics: piroxicam

Piroxicam is an oxicam non-steroidal anti-inflammatory drug (NSAID). Its plasma half-life has been estimated at 45 h (allowing once-daily dosage), with the peak plasma concentration occurring 2–4 h after oral administration [1]. Several studies have demonstrated its efficacy as an analgesic following dental extractions or minor dental surgery such as removal of impacted third molars.

Piroxicam in single doses of 20 or 40 mg has been shown to produce analgesia equivalent to or better than that produced by aspirin 648 mg (single dose) [2–5], mefenamic acid 500 mg (single dose) [6] or acetaminophen 500 mg (8-hourly, three doses) [7]. Three studies have demonstrated that, compared with aspirin, piroxicam produces peak analgesia more slowly [2–4], although Ohnishi, Kawai and Ogawa detected no difference in the time of onset of analgesia when comparing piroxicam with mefenamic acid [6]. Several investigators have noted the prolonged analgesia resulting from a single dose of piroxicam [2–4, 7–9]. Parsloe and colleagues demonstrated that the analgesic effects of a single dose of piroxicam 40 mg persisted into the 3rd day after operation [9].

None of the above studies reported any symptoms of peptic ulceration, bronchospasm or generalized allergy associated with the use of piroxicam.

One disadvantage of piroxicam as a postoperative analgesic is its slower onset of action compared with other oral agents and alternative routes of administration. This difficulty may be overcome by preoperative administration of the drug. Piironen, Sjöblad and Oikarinen [10] studied the effects of piroxicam 20 mg administered either before or 3 h after surgery, in patients undergoing extraction of an impacted lower third molar under local anaesthesia. Postoperative pain scores at 2, 3 and 4 h were significantly lower in the group who had received preoperative medication.

The present study was designed to investigate the preoperative use of piroxicam in patients undergoing the surgical removal of lower third molars under general anaesthesia.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. All patients gave informed consent before participation in the trial.

We studied 50 patients undergoing surgical removal of lower third molars under general anaesthesia (some patients were also undergoing additional extractions). Exclusion criteria were: history of asthma or peptic ulceration, or other upper GI pathology; pregnancy or breast feeding;

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allergy to aspirin or other NSAID and any contraindication to the standard anaesthetic technique used.

Premedication was administered 2.5 h before the estimated time of surgery: patients received either two capsules of piroxicam 20 mg or two placebo capsules, prepared and allocated randomly by the hospital pharmacy. Placebo and active capsules were identical in appearance. The timing of this premedication was chosen to ensure that as many patients as possible recovered from anaesthesia between 2 and 4 h after drug administration, during the peak effect of the piroxicam. The investigators were unaware of the nature of the capsules received by the patients until the study ended. No other premedication was given.

All patients were anaesthetized in a standard manner. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was then administered, a nasotracheal tube passed, and the throat packed. Anaesthesia was maintained with 2 % isoflurane in nitrous oxide (6 litre min^{-1}) and oxygen (3 litre min^{-1}) via a Bain circuit, with the patient breathing spontaneously.

When surgery was completed, the inhalation agents were discontinued and a stop-clock started. This clock was taken with the patient to the recovery area, and was switched off when the patient first responded to command. In this way, the duration of recovery was measured. The time at which the patient received the premedicant drug, the time at which anaesthesia was induced and the time at which the anaesthetic was stopped were also recorded and, at a postoperative visit, the time at which analgesia was first received was noted, together with the total number of analgesic doses required in the first 24 h after operation.

The durations of three other time intervals were calculated: anaesthetic time (induction to end of anaesthesia); dose–recovery time (premedication to response to command); recovery–analgesia time (recovery to first analgesia).

A standard regimen of postoperative analgesia was prescribed: i.m. papaveretum 15 mg (female, small male) or 20 mg (male, large female) 4-hourly as required, and oral paracetamol 1 g 6-hourly as required. Analgesia was provided by the nursing staff on request, within the limits of this prescription. Patients had been informed that paracetamol tablets were available for pain relief, and that a powerful, injectable analgesic was available also if they felt that paracetamol would be inadequate.

Nausea and vomiting were treated with i.m. prochlorperazine 12.5 mg, if necessary.

Statistical analyses

Normally-distributed data (age, anaesthetic time, recovery time and dose–recovery time) were analysed using Student's *t* test. Sex distributions were compared using a chi-square test.

The number of paracetamol doses required in the first 24 h was analysed using the Mann–Whitney *U* test, and a chi-square test was performed to compare the number of patients in each group who did not require opioid analgesia.

Recovery–analgesia times were treated as being analogous to survival data. "Survival" curves were plotted to indicate the proportion of patients in each group who had received no analgesia by a given time after operation, and the recovery–analgesia times for the two groups were compared using the log rank test (this compares the observed rate at which patients requested analgesia with the rate which might be expected if piroxicam and placebo were equally effective [11]).

RESULTS

Of the patients who were otherwise suitable for inclusion in the study, three were excluded because of a history of asthma, and four because of documented peptic ulceration. Two other patients refused to participate.

One patient agreed to take part in the study, but was unable to swallow the capsules. She was later found to have been assigned to the placebo group. Twenty-four patients therefore remained in the placebo group, and 25 received active medication.

There were no significant differences in age and sex distribution, anaesthetic time, recovery time or dose–recovery time between active and placebo groups (table I). The measured dose–recovery times occurred between 2 and 4 h for all but one of the patients who received piroxicam (this patient recovered 263 min after her dose had been

TABLE I. *Demographic and anaesthetic data for the active and placebo groups (mean (SD))*

	Piroxicam	Placebo
Sex (M/F)	10/15	7/17
Age (yr)	24.2 (5.1)	24.1 (5.0)
Anaesthetic time (min)	28.3 (10.7)	29.1 (8.2)
Recovery time (min)	9.4 (2.4)	9.8 (2.6)
Dose–recovery time (min)	194.5 (27.0)	194.9 (35.2)

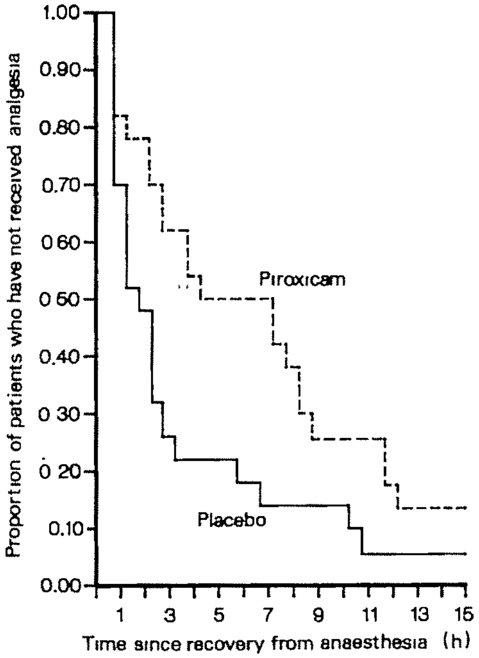

FIG. 1. "Survival" curves for the active and placebo groups, representing the proportion of patients in each group who had not required any analgesia since recovery from anaesthesia.

administered). Three patients in the placebo group had dose–recovery times which exceeded the target range (up to 272 min).

Recovery–analgesia times were longer in the piroxicam group (median 393 min, range 18 min to >24 h) than in the placebo group (median 199.5 min, range 6 min to >24 h) (log rank test, $P < 0.05$). Recovery–analgesia times are displayed in the form of "survival" curves in figure 1. The curves indicate the proportion of patients in each group who had received no analgesia by a given elapsed time since recovery from anaesthesia. (Those patients who had not requested analgesia by 15 h after recovery continued without needing analgesia for the full 24 h of the study.)

Significantly fewer patients in the piroxicam group required opioid analgesia (chi-square test, $P < 0.05$), and the piroxicam group also received fewer doses of paracetamol than the placebo group (one-tailed Mann–Whitney U test, $P < 0.05$) (table II).

The data for the patients who required opioids after surgery were examined separately, in an effort to identify possible causes of additional analgesic needs. In both the piroxicam and the placebo group there was no significant difference, in terms of duration of anaesthesia or dose–recovery time, between patients who required opioids and those who did not.

TABLE II. *Number of patients requiring 0–2 doses of papaveretum or 0–4 doses of paracetamol in the first 24 h after recovery from anaesthesia*

Number of doses	Number of patients Piroxicam	 Placebo
Papaveretum		
0	19	11
1	6	11
2	0	2
Paracetamol		
0	4	2
1	10	4
2	6	10
3	4	6
4	1	2

DISCUSSION

Premedication was timed successfully to allow patients to recover from anaesthesia during the peak effects of piroxicam, or shortly thereafter. Patients who received piroxicam and also required postoperative opioids had dose–recovery times similar to other patients in their group. The need for opioid analgesia was unrelated to the timing of premedication or the duration of anaesthesia and surgery. This bears out the results of Parsloe and colleagues [9], who found no relationship between postoperative pain and the duration or difficulty of surgery.

Piroxicam was shown to have no significant effect on the duration of recovery from anaesthesia, as might be expected from its non-sedative nature.

Parsloe and others have conducted a similar study [9], allocating patients randomly to receive preoperative piroxicam or placebo, combined with halothane or isoflurane anaesthesia (four groups in all). Opioid analgesia was prescribed in an "on request" manner, and visual analogue pain scores were recorded at 2, 4 and 18 h after surgery. A significant difference in analgesic requirement was detected between two of the groups, but pain scores were not significantly different.

In our study, analgesia was also prescribed on request. A comparison of pain scores would have been valid only during the period immediately after recovery, before any of the patients had received analgesia. During this time, a patient who is obviously in pain may be unable to record a visual analogue pain score. Under these circumstances, the patients' requirements for analgesia appear to give a better indication of the severity of their pain, therefore pain scores were not assessed.

Parsloe's group [9] did not demonstrate any reduction in postoperative requirement for opioid which could be ascribed to piroxicam alone. In the first 18 h after operation, patients who had received piroxicam and isoflurane required significantly less analgesia than those who had received piroxicam and halothane or placebo and halothane. A synergistic effect between piroxicam and isoflurane was postulated to explain this observation. However, no significant differences in analgesic requirements could be detected between the piroxicam with isoflurane and placebo with isoflurane groups, or between the piroxicam with halothane and placebo with halothane groups. Lack of significance may have been because of the small number of patients in each group (15).

By examining larger numbers of patients in each group, we were able to detect a significant effect of piroxicam on postoperative opioid requirement. The proportion of patients in each group who required opioids was similar to the corresponding proportions found by Parsloe and colleagues in their isoflurane groups. In the current study, 24% of the patients who received piroxicam and 54% of those who received placebo required opioids after operation. Corresponding figures from Parsloe's study were 27% and 60%, respectively. This similarity is striking, as Parsloe used an anaesthetic technique similar to that used here, apart from the addition of papaveretum 5–7.5 mg, given just before induction of anaesthesia. Their use of opioids during operation appeared to have had little effect on postoperative requirements for analgesia.

While significant differences in paracetamol requirements and recovery–analgesia times were detected, the most important finding of the present study was the opioid-sparing effect of piroxicam premedication.

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SPINAL ANAESTHESIA WITH PLAIN 0.5% BUPIVACAINE AT 19 °C AND 37 °C

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H. C. HUSEGAARD AND I. ZÜLOW

SUMMARY

Forty-five men aged 50–80 yr undergoing urological surgery under spinal anaesthesia were allocated randomly to three groups. All patients received 0.5% plain bupivacaine 3 ml injected at the L2–3 interspace. The temperature of the solution in group 1 was 19 °C, in groups 2 and 3 37 °C. In groups 1 and 2 the injection was performed with the patient sitting; in group 3 the patient was in a lateral horizontal position. Spread of block, intensity of motor block and cardiovascular stability were measured. Warming the solution from 19 °C to 37 °C before spinal injection with the patient in the sitting position did not significantly affect these variables. However, the extent of analgesia was reduced significantly when the 37 °C solution was injected with the patient in the lateral horizontal compared with the sitting position.

KEY WORDS

Anaesthetics, local: bupivacaine, injectate temperature. Anaesthetic techniques, spinal.

Factors expected to influence spread of spinal analgesia have been studied intensively by several groups [1–9]. However, temperature of injected anaesthetic solutions has not received much attention until recently.

In 1988, Beardsworth and colleagues reported that the temperature of a solution injected into a spinal canal model affected its distribution [10]. In a clinical study with 0.5% plain bupivacaine, Stienstra and van Poorten injected solutions at temperatures of 4 °C and 37 °C with patients sitting. They found a significantly higher cephalad spread of analgesia in the 37 °C group [11]. In a recent study, Beardsworth and Lambert injected the solutions at 37 °C and 20 °C, but with the patient in the horizontal position. They found no difference in cephalad spread of analgesia, but a longer duration after injection of solution at body temperature [12].

The purpose of this study was to evaluate the clinical effect of using a solution of 0.5% plain bupivacaine at 37 °C instead of room temperature, injected in the sitting patient.

PATIENTS AND METHODS

We studied 45 men (ages 50–80 yr) undergoing cystoscopy or transurethral resection of the prostate. None of the patients suffered from neurological disease or deformity of the spine, and no patient had a history of hypersensitivity to local anaesthetics. Informed consent was obtained from all patients, and the study was approved by the local Ethics Committee.

The patients were allocated randomly to three groups, each of 15 patients. All received plain 0.5% bupivacaine 3 ml over 30s after lumbar puncture at the L2–3 interspace with a 25-gauge needle. Before this procedure isotonic saline 500 ml was infused i.v.

In group 1 the temperature of the anaesthetic solution was 19 °C (room temperature), and the injection was performed with the patient sitting. The patient was kept sitting for 2 min and then placed in the lithotomy position. In group 2 the temperature of the anaesthetic solution at in-

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TABLE I. *Patient data: mean* (SD) *age, height and weight. No significant differences between groups*

	Group 1 (19 °C, sitting)	Group 2 (37 °C, sitting)	Group 3 (37 °C, horizontal)
Number	15	15	15
Age (yr)	70.1 (7.7)	67.8 (7.0)	69.5 (7.1)
Height (cm)	173.2 (5.0)	173.3 (6.2)	172.3 (7.8)
Weight (kg)	74.2 (12.1)	78.3 (10.3)	81.3 (15.1)

TABLE II. *Maximum cephalad spread of analgesia, thoracic segments (median values (range)). In group 3, range (0–10) indicates segments C8–T10.* *$P < 0.05$ *between groups 2 and 3*

Maximum spread	Group 1 (19 °C, sitting)	Group 2 (37 °C, sitting)		Group 3 (37 °C, horizontal)
Thoracic dermatome	5.4 (3–10)	4.6 (2–8)	*	6.3 (0–10)

jection was 37 °C (body temperature) after temperature equilibration in water, and the position identical to that of group 1. In group 3 the temperature of the anaesthetic solution was 37 °C and injection was performed with the patient in the lateral horizontal position. The patient was placed immediately in the supine position, and after a further 2 min, in the lithotomy position.

Arterial pressure was measured at 5-min intervals and ECG was monitored continuously.

The cephalad spread of analgesia was assessed as the dermatomal segment in which sensation to midline pinprick was lost, characterized by incomplete analgesia. Motor block was assessed by the Bromage scale (scores 3–0). Testing was performed 5, 10, 15, 20 and 30 min after administration of bupivacaine, and thereafter every 30 min until sensory block had recovered to T10 level. All patients were tested for at least 120 min. The investigator undertaking these tests was unaware of the temperature of the anaesthetic solution and the initial positioning of the patient.

Side effects were noted, and ephedrine 5 mg was administered i.v. if systolic arterial pressure decreased by more than 25%. All statistical comparisons were made between group 1 and group 2 (different temperature) and between group 2 and group 3 (different posture) using the Mann–Whitney non-parametric test. $P < 0.05$ was taken as significant.

RESULTS

There were no significant differences between the three groups in patient age, height or weight (table I).

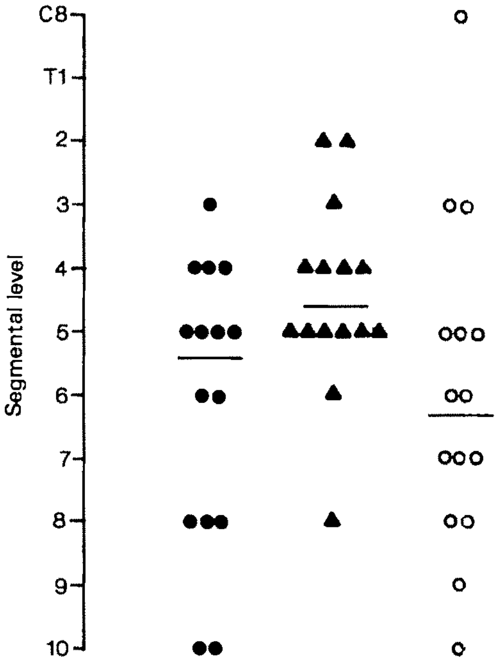

FIG. 1. Maximal cephalad spread of analgesia in groups 1 (●), 2 (▲) and 3 (○). Horizontal bars represent median values.

Cephalad spread of analgesia

The most extensive cephalad spread of analgesia was seen in group 2 and the least in group 3 (table II, fig. 1). The difference was significant only between these two groups. Nevertheless, the patient in whom analgesia reached the highest segmental level (C8) was in group 3. Generally, the range was larger and the predictability lower

TABLE III. *Duration of complete analgesia in segmental levels T6–10 (median values (range)).* * $P < 0.05$ *between groups 2 and 3*

Dermatome	Group 1 (19 °C, sitting)	Group 2 (37 °C, sitting)		Group 3 (37 °C, horizontal)
T10	110 (0–276)	155 (38–221)		122 (0–199)
T8	69 (0–191)	123 (0–171)	*	40 (0–168)
T6	50 (0–110)	63 (0–149)	*	0 (0–123)

TABLE IV. *Maximal decrease in systolic arterial pressure during the first 30 min (median values (range)). No significant differences*

	Group 1 (19 °C, sitting)	Group 2 (37 °C, sitting)	Group 3 (37 °C, horizontal)
Pressure decrease (% of initial value)	14 (0–35)	21 (0–49)	15 (2–30)

in this group compared with the others. The smallest range was found in group 2.

Duration of analgesia

The duration of analgesia in segmental levels T6–10 was marginally longer in group 2 than in groups 1 and 3 (table III). At the T10 level the differences were not significant, but at the other levels tested the differences between group 2 and 3 were significant.

In all groups the range was very large, and complete analgesia at the T10 level was obtained by every patient only in group 2. All groups contained patients without analgesia at the T6 and T8 levels (table III).

Motor block

Scale 3 block or total paralysis was seen in 14 of 15 patients in both groups 1 and 3. In group 2 this was obtained in 13 of 15 patients.

Cardiovascular stability

The decrease in systolic arterial pressure during the first 30 min was most pronounced in group 2, but this was not significant (table IV). Consumption of ephedrine did not differ in the three groups. No patient developed major cardiovascular or pulmonary problems.

DISCUSSION

Extent of analgesia after subarachnoid injection of plain bupivacaine has been shown to be affected primarily by total dose [2, 3] and other factors have been thought to be of minor importance [2–4, 7–9]. Stienstra and van Poorten reported that changing the temperature of plain bupivacaine modified analgesia considerably [11]. However, the clinical relevance of this study was limited, as a temperature of 4 °C is probably not used in clinical practice. They found significantly greater cephalad spread and smaller variance in the 37 °C group, when the injection was performed with the patient in the sitting position. The authors postulated that the temperature effect was caused by difference in baricity, although it was admitted that this was small [11]. Our results are at variance with these data, but it must be emphasized that the studies differed in several ways.

We found only minor and non-significant differences in maximal cephalad spread of analgesia between group 1 (19 °C, sitting position) and group 2 (37 °C, sitting position), and the same pattern was seen for duration of analgesia in segments T6–10, intensity of motor block and cardiovascular stability. However, cephalad spread of analgesia was approximately one segment higher and the duration 10–50 min longer when the warm solution was injected. It must be emphasized that regression of analgesia below T10 was not monitored consistently. In accordance with the data of Stienstra and van Poorten [11], the variability seemed to be smaller in group 2 than group 1, possibly because the time for temperature equilibration was an important factor influencing the spread of analgesia in the latter group. The difference in cephalad spread in the two studies may be explained by greater difference in temperature of the solutions used by Stienstra and van Poorten.

Recently, Stienstra and colleagues have examined the use of 0.5% plain bupivacaine at temperatures of 20 °C and 37 °C [13]. The solutions were injected with the patients in the sitting position. They reported a significantly higher maximal cephalad spread and longer duration of analgesia with the warm solution. These data cannot be confirmed by our study. In the Dutch study, patients were kept sitting for longer after the injection was completed, and this may be responsible for some differences in spread of analgesia.

Comparing group 2 (37 °C, sitting position) and group 3 (37 °C, horizontal position) we found significant differences in maximal cephalad spread and a greater variance in group 3. Thus the warm solution may be slightly hypobaric, with more unpredictable spread when injected with the patient in the lateral horizontal position. Our data support the view that the baricity of the solutions used by Stienstra and van Poorten was responsible at least partly for the different spread observed [11]. Movement of a hypobaric solution in the horizontal spinal canal would be expected to be dependent on the extent of individual spinal curvature, and this probably explains the large variability in group 3.

The duration of analgesia in the higher segmental levels (T6–8) was significantly longer in group 2 than in group 3, but no difference was found in duration at T10, or in motor block or cardiovascular stability between the two groups. According to Beardsworth and Lambert, duration of analgesia should be increased by warming a spinal solution, but in their study injections were made always with the patient in the lateral horizontal position [12]. Thus their study and ours are not directly comparable.

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EFFECT OF EXTRADURAL COMPLIANCE AND RESISTANCE ON SPREAD OF EXTRADURAL ANALGESIA

Y. HIRABAYASHI, R. SHIMIZU, I. MATSUDA AND S. INOUE

SUMMARY

We have studied the effect of extradural compliance and extradural resistance on the spread of extradural analgesia. In 111 patients aged 21–75 yr, compliance and resistance of the extradural space were calculated by a mathematical analysis (using the Windkessel theory) of the extradural pressure–response curve to injection of a given volume of local anaesthetic. The calculated mean extradural compliance was 0.39 (SD 0.13) ml mm Hg^{-1} and this increased with advancing age ($P < 0.01$). The total number of analgesic segments blocked was related to extradural compliance ($P < 0.01$). Segmental dose requirement was related inversely to extradural compliance ($P < 0.01$). Calculated extradural resistance was 26.8 (14.5) mm Hg s ml^{-1} and this decreased with advancing age ($P < 0.05$). The total number of analgesic segments blocked was related inversely to extradural resistance ($P < 0.05$). Segmental dose requirement was related to extradural resistance ($P < 0.05$).

KEY WORDS

Anaesthetic techniques: extradural

The changes in extradural pressure caused by extradural injection of local anaesthetics have been thought to affect the spread of injected solution in the extradural space [1]. Despite the recognition that extradural compliance and resistance are related to the extent of analgesia, few controlled studies of these variables have been made [2, 3]. Our previous studies performed under standardized conditions in which local anaesthetics were injected into the extradural space at constant pressure [4] or speed [5], led us to believe that smaller changes in extradural pressure caused by extradural injections of local anaesthetics results in increased spread of extradural analgesia.

We have studied the effect of extradural compliance or extradural resistance on the spread of extradural analgesia. Using the Windkessel theory [6] in a mathematical analysis of the extradural pressure–response curve to a given volume of local anaesthetic, we have measured the compliance and the resistance of the extradural space.

METHODS

Mathematical analysis

A pressure curve obtained during and following rapid extradural injection of local anaesthetic consists of two parts: the first part of the pressure curve occurs while the injection is delivered and the second one occurs after the injection has terminated (fig. 1). The first part (expansion of the extradural space induced by a given volume of fluid) is often termed the "forced response curve", whereas the second part is often termed the "free response curve" [6]. The speed of injection plays a major role in determining the forced response curve. Extradural compliance and resistance play important roles in determining both the forced response curve and the free.

We considered that the extradural pressure (P) may obey the following relationship through the Windkessel theory:

$$C\cdot\frac{dP}{dt}+\frac{1}{R}\cdot P=i$$

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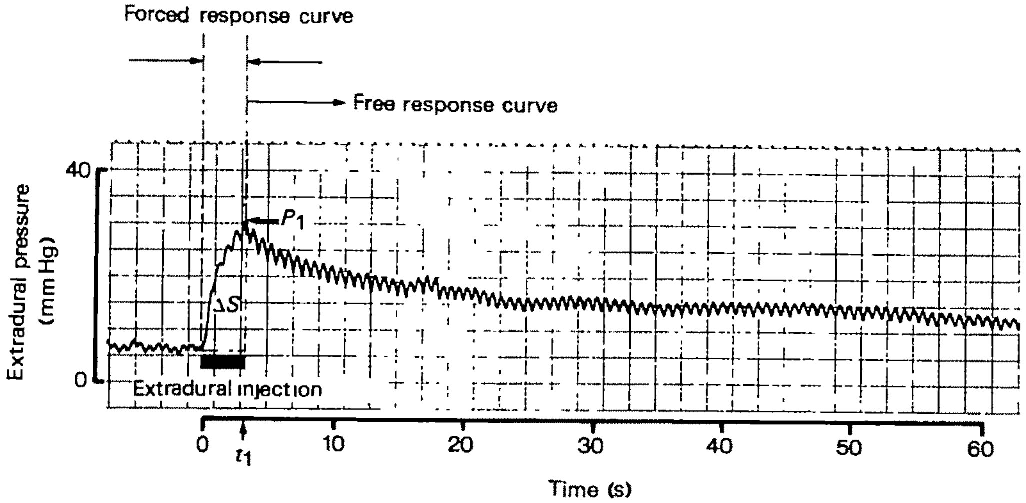

FIG. 1. Typical extradural pressure–response curve obtained during and following the extradural injection of 2% mepivacaine 10 ml.

where C = extradural compliance, dP/dt = first derivative of extradural pressure with time, R = extradural resistance and i = speed of injection.

Integrating with respect to time, this becomes:

$$C\int_0^{t_1}\left(\frac{dP}{dt}\right)dt+\frac{1}{R}\cdot\int_0^{t_1}P\,dt=\int_0^{t_1}i\,dt \qquad (1)$$

where t_1 = injection time, $\int_0^{t_1}(dP/dt)dt$ = peak extradural pressure measured at termination of injection (P_1), $\int_0^{t_1}P\,dt$ = area under the forced response curve (ΔS), and $\int_0^{t_1}i\,dt$ = total volume of injected solution (ΔV).

The free response curve occurs when the extradural space is not expanded and therefore it may be related primarily to the properties of the extradural space [7]. A straight line can be obtained by plotting pressure in the free response curve on a natural logarithmic axis against time. Therefore, extradural pressure of the free response curve obeys the following relationship:

$$P=P_1\cdot e^{-\frac{t}{T}}$$

where T = time constant, and may be determined by the least square method from the pressure values in the free response curve. The following equation is obtained from equation (1) referring to $T = CR$:

$$C=\frac{\Delta V}{P_1+\frac{1}{T}\cdot\Delta S} \qquad (2)$$

Resolving equation (1) for R on referring to $T = CR$:

$$R=\frac{1}{\Delta V}\cdot(T\cdot P_1+\Delta S) \qquad (3)$$

Patients

We studied 111 patients aged 21–75 yr, requiring extradural analgesia for extracorporeal shock wave lithotripsy. Informed consent was obtained from each patient. Patients who had the following diseases were excluded: central nervous system disease, lumbar disc surgery, abnormalities of the vertebral column, abdominal distension caused by intestinal obstruction, ascites, tumour or pregnancy, and bleeding diathesis. Premedication comprised atropine 0.5 mg i.v. just before the extradural injection. The patient was placed in the right lateral position on a horizontal operating table. A 17-gauge Tuohy needle with the bevel pointing caudad was inserted into the extradural space at the T12–L1 interspace via a mid-line approach. The extradural space was identified by the "dripping infusion" method [8]. After the extradural space was identified, extradural pressure was measured continuously using a transducer (Yokokawa Hewlett Packard 78242A) calibrated (mm Hg) via a three-way tap. A second Tuohy needle with the bevel pointing cephalad was inserted subsequently into the extradural space at the L1–2 interspace via a mid-line approach. The extradural space was identified by

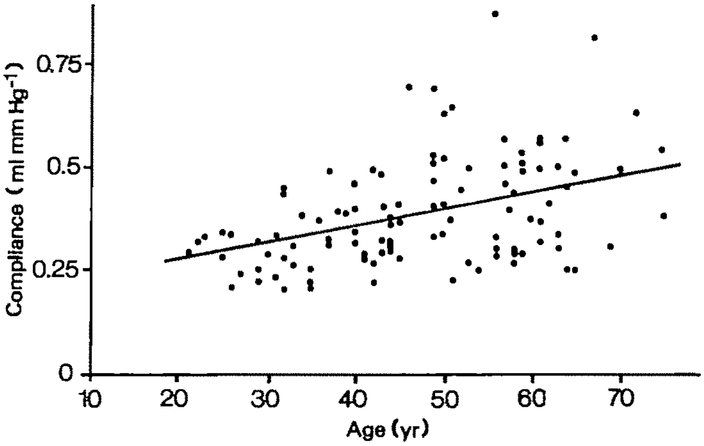

FIG. 2. Correlation between age and extradural compliance ($r = 0.40$; $y = 0.00406x + 0.20145$; $P < 0.01$).

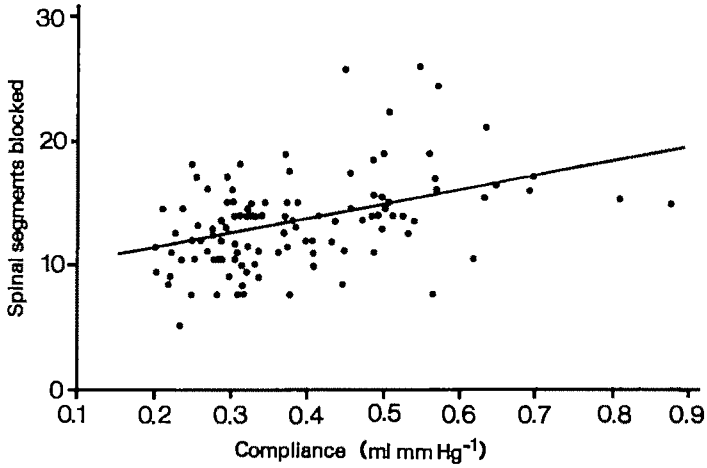

FIG. 3. Correlation between extradural compliance and extent of analgesia ($r = 0.40$; $y = 11.44x + 9.09$; $P < 0.01$).

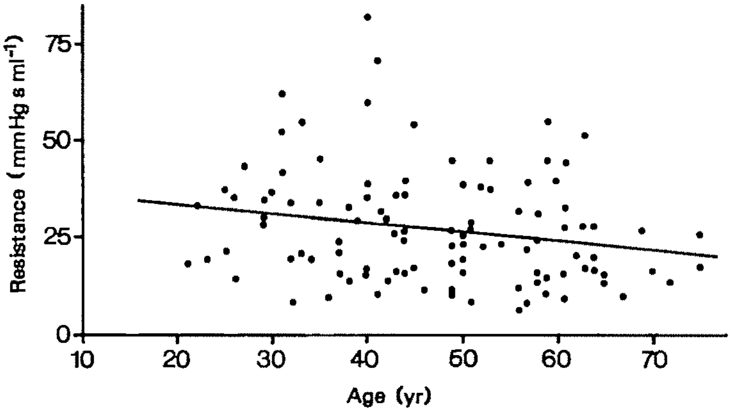

FIG. 4. Correlation between age and extradural resistance ($r = -0.22$; $y = -0.24x + 38.10$; $P < 0.05$).

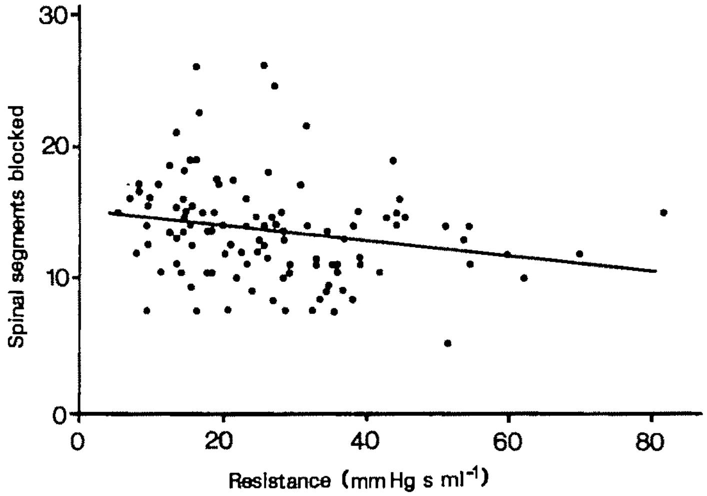

FIG. 5. Correlation between extradural resistance and extent of analgesia ($r = -0.22$; $y = -0.058x + 15.12$; $P < 0.05$).

the loss of resistance method. Before injection of local anaesthetic, the extradural pressure was allowed to equilibrate with atmospheric across the second Tuohy needle. When no cerebrospinal fluid or blood was aspirated through the second Tuohy needle, 10 ml of 2% mepivacaine (without adrenaline) was rapidly injected manually (mean injection time 2.3 (SD 0.7) s). The pressure curve obtained via the first Tuohy needle during each extradural injection and the pressure curve following completion of the injection were recorded continuously for 60 s on a recorder (Yokokawa Hewlett Packard 78172A) at a paper speed of 2.5 mm s^{-1}. An extradural catheter was then introduced and the patient turned to the supine position. Fifteen minutes after the extradural injection, the upper and lower extent of analgesia to pinprick was assessed [9]. The extent of analgesia was expressed by the average number of analgesic segments on each side. The volume of 2% mepivacaine required to block one spinal segment (segmental dose requirement) was calculated.

The relationships between extradural compliance or extradural resistance and the extent of analgesia were analysed by correlation coefficients. $P < 0.05$ was considered significant. Regression lines were calculated by the method of least squares.

RESULTS

The calculated mean extradural compliance was 0.39 (0.13) ml mm Hg^{-1}; this increased with advancing age ($r = 0.40$, $P < 0.01$) (fig. 2). The total number of analgesic segments was related to extradural compliance ($r = 0.40$, $P < 0.01$) (fig. 3). The segmental dose requirement was related inversely to extradural compliance ($r = -0.37$, $P < 0.01$).

The calculated extradural resistance was 27.1 (14.5) mm Hg s ml^{-1}; this decreased with advancing age ($r = -0.22$, $P < 0.05$) (fig. 4). The total number of analgesic segments was related inversely to extradural resistance ($r = -0.22$, $P < 0.05$) (fig. 5). The segmental dose requirement was related to extradural resistance ($r = 0.21$, $P < 0.05$).

DISCUSSION

This study has shown that the compliance and the resistance of the extradural space influenced the spread of solutions injected into the extradural space. We found that the greater the compliance and the smaller the resistance, the greater was the spread of extradural analgesia. Generally, more extensive analgesia was obtained by a small dose of anaesthetic solution in the elderly. This may be related to the fact that the extradural compliance increased and the extradural resistance decreased with advancing age.

The extradural space is a potential space [10] limited by the dura internally and by the connective tissue lining the space externally. It is regarded as a partially rigid but leaky container within which many elastic components are involved [1]. An analogy may be made with a compartmental system with compliant and resistant properties, especially when it is expanded with a given volume of fluid. When a semilogarithmic plot of the free response curve has linear characteristics as shown in figure 1, this system has a first-order response with a time constant of T, and it may be characterized as one with compliance and resistance. Unfortunately, there is no direct way of measuring compliance and resistance of the extradural space. Application of the Windkessel theory to pulsatile injection of fluid into the extradural space is an indirect approach.

When a local anaesthetic is injected into the extradural space, initially it fills the space adjacent to the inserted needle, and creates pressure in the space. It may also create cephalad movement of CSF. Subsequently, injected solution travels along paths of least resistance. We postulated that the fatty tissue in the extradural space may play an important role in determining longitudinal spread of anaesthetic solution. The extradural space in young subjects is packed tightly with rigid fat [11] and has low compliance and high resistance; therefore, less longitudinal spread of injected solution occurs. As the fatty tissue degenerates with advancing age, the extradural space becomes more compliant and less resistant; therefore, greater longitudinal spread of injected solution occurs.

Our findings differ from the views of Bromage [1]. Based on the work of Usubiaga, Wikinski and Usubiaga [2], he considered that extradural compliance decreases with advancing age. Usubiaga's group measured the changes in extradural pressure following manual injection of lignocaine and showed that the higher residual positive pressure 2 min after completion of the injection resulted in increased spread of analgesia. They speculated that residual positive pressure is dependent on the patency of the intervertebral foramina. However, our previous studies (performed under standardized conditions in which 15 ml of mepivacaine was injected at constant pressure (80 mm Hg) [4] or at constant speed (1 ml s^{-1}) [5]) did not show any significant correlation between the residual pressure 1 min after the injection and the extent of analgesia or the patient's age. Our findings were confirmed by a recent study which examined extradural pressure 1 min after injection of two different volumes of bupivacaine [3].

The reasons for the difference between Usubiaga's study and ours are not clear, but may be related to the fact that they measured residual pressure only 2 min after manual injection and the values for peak pressures were highly variable, whereas we examined changes in extradural pressure recorded continuously in response to a standardized automated injection. Anatomical studies in cadavers have suggested recently that the volume which spills out through the lateral intervertebral foramina is independent of their permeability, because lateral spread is confined to the area of cuffs surrounding spinal nerves [12] and because the displacement of CSF may act as a safety valve which limits the increase in extradural pressure [3].

In order to obtain accurate pressure–response curves, we injected local anaesthetics more rapidly than occurs in routine clinical practice. The forced response curve demonstrated a sharp increase at the rapid injection; the area under this curve (ΔS) was small and, therefore, the compliance and the resistance of the extradural space calculated by equations (3) and (4) should have a small error. Although rapid injection may cause patient discomfort and it is necessary to guard against the possibility of increased risk of local anaesthetic toxicity, this method permits measurement of both compliance and resistance of the extradural space, and it obviates inaccuracies observed in techniques using slow rates of injection.

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EFFECTS OF NIMODIPINE ON CEREBRAL BLOOD FLOW AND NEUROPSYCHOLOGICAL OUTCOME AFTER CARDIAC SURGERY

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SUMMARY

Thirty-five patients undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) were allocated randomly in a prospective double-blind study to receive either nimodipine 0.5 $\mu g\ kg^{-1}\ min^{-1}$ or placebo. Cerebral blood flow (CBF) was measured during and immediately after CPB. Neuropsychological tests were performed 6 months after surgery to determine any relationship between ischaemic damage and CBF and administration of nimodipine. There were no differences in CBF between the nimodipine (n = 18) and placebo groups (n = 17). Significant changes in neuropsychological tests were found in six patients tested 6 months after surgery but there were no conclusive signs of ischaemic damage. The nimodipine-treated group performed better in tests of verbal fluency and visual retention, suggesting that some memory functions were preserved better in this group.

KEY WORDS

Brain· cerebral blood flow. Heart: calcium channel blocker, nimodipine.

The incidence of neurological sequelae after cardiac surgery varies from 1.3% to 79% [1–3]. Several studies have examined intraoperative factors associated with poor neurological outcome [4–7]. These include reduced cerebral perfusion pressure (CPP) during cardiopulmonary bypass (CPB) [5], and some postmortem studies have shown lesions in the boundary territories between major cerebral arteries, indicating hypotensive ischaemia [6]. Particulate or air emboli from the bypass circuit may also cause localized ischaemia [7].

Development of ischaemic damage has been linked to an increase in intracellular free Ca^{2+} during ischaemia reducing further cerebral blood flow (CBF) and inducing deleterious intracellular events including breakdown of phospholipids, production of free oxygen radicals and release of excitatory amines [8, 9].

The calcium channel blocker nimodipine has been reported to increase CBF both in regional cerebral ischaemia [10] and in the period of reduced flow after resuscitation from cardiac arrest in man [11].

This study was designed to determine if nimodipine has any influence on CBF during and shortly after CPB and if it reduces the incidence of cerebral damage as measured by neuropsychological testing.

PATIENTS AND METHODS

This prospective study was approved by the Institutional Ethics Committee, the Norwegian Council for Science and the Humanities and the Norwegian Medicine Control Authority. Informed consent to participate in the study was received from 39 patients undergoing replacement of the mitral or aortic valve, coronary artery bypass grafting (CABG), or any combination of these procedures. Patients with known cerebral, cerebrovascular or psychiatric disorders were excluded.

Neuropsychological tests were performed by the same neuropsychologist (B.T.O.) on the day before surgery and within 5 days and 6 months

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TABLE I. *Neuropsychological tests used, number of test variables and main function tested*

Test name	Number of variables	Tested function
Mental state		
Jacobs [12]	4	Organic mental screening
PASAT [13]	1	Information processing
Trail-making [14]	2	Conceptual shifting, verbal mediation, perceptual motor speed
Verbal fluency [15]	2	Word production, associative memory
Memory tests		
Bentons visual [16]	8	Visual retention test
Lurias methods [17]	7	Verbal learning, distractability
Verbal digit span [18]	2	Short memory test
Motor tests		
Digit symbol [19]	1	Motor speed, perception
Zazzo [19]	4	Motor speed, perseveration tendency

after surgery. Thirty-one test variables were used, testing mental state, memory, psychomotor performance and sustained attention (table I) [12–19].

All patients received pethidine 1 mg kg^{-1} and promethazine 0.5 mg kg^{-1} i.m. 1 h before operation. All anaesthetic procedures were performed by anaesthetists not involved in the study.

Anaesthesia was induced with fentanyl 0.01–0.02 mg kg^{-1} and diazepam 0.1–0.2 mg kg^{-1} and maintained with 50% nitrous oxide in oxygen and additional doses of fentanyl 0.2–0.4 mg and diazepam 2.5–5 mg as needed. Neuromuscular block was produced with pancuronium 0.1 mg kg^{-1} and maintained with additional doses of 2 mg when needed.

Ventilation of the lungs was adjusted to keep Pa_{CO_2} at 4.6–5.6 kPa at the actual patient temperature (oesophageal). A pulmonary artery and a radial artery catheter were used for measuring haemodynamic variables.

Hypotension, defined as a reduction in mean arterial pressure (MAP) of 20% less than pre-anaesthetic values, if it occurred before CPB, was treated with an infusion of crystalloids, while that during weaning from CPB and after CPB was treated with dopamine, adrenaline or both.

CPB was performed in a non-pulsatile mode using a roller pump (Polystan) and a bubble oxygenator (Polystan 011500). A 30-µm filter (Polystan standard) was used in the cardiotomy suction and a depth filter (Cobe, U.S.A.) in the arterial cannula. The pump flow was set initially at 2.4 litre min^{-1} m^{-2} and reduced to 2.0 litre min^{-1} m^{-2} during hypothermia (30 °C).

CBF was measured (fig. 1) after sternotomy and during hypothermic CPB (30 °C). An i.v. infusion of nimodipine 0.5 µg kg^{-1} min^{-1} or placebo (the solvent for nimodipine, each 10 ml containing ethanol 1.5 g, polyethylene glycol (400) 1.5 g, sodium citrate 0.02 g, citric acid 0.003 g and water 7 g) was thereafter started in a randomized, blinded fashion. Further measurements were performed 15 and 45 min later, after CPB when the circulation was stable and 15 min after the infusion had been discontinued.

In the first 10 patients (six nimodipine, four placebo) CBF before and after bypass was measured by xenon clearance. After i.v. injection of xenon-133 15–20 mCi, clearance was measured

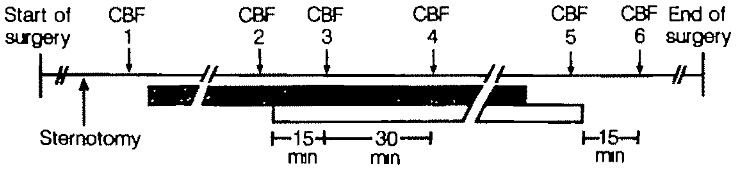

FIG. 1. Timing of cerebral blood flow (CBF) measurements in relation to start of surgery, cardiopulmonary bypass period (▨) and infusion of study drug (nimodipine/placebo) (☐).

by five external scintillation detectors positioned over the right parietal hemisphere. An air detector sampled expired air for assessment of arterial and air xenon-133 activity using a Novo Cerebrograph 10a (Novo, Hadsund, Denmark). CBF was determined from the initial slope index as described by Risberg and colleagues [20]. During CPB, xenon-133 was injected in a catheter positioned in the right common carotid artery via the brachiocephalic trunk. CBF was then measured by the method of Olesen, Paulsen and Lassen [21]. All measurements were corrected for background or remaining activity and for changes in the xenon-133 tissue:blood partition coefficient, caused by variations in temperature and packed cell volume (PCV) [22].

The i.v. technique was abandoned after the first 10 patients as it was felt that the need for 11 min of surgery without diathermy was incompatible with optimal patient care. In the remaining patients, all CBF measurements were performed by the intra-arterial method, requiring only 1 min without diathermy.

Cerebral vascular resistance index (CVRI, mm Hg ml^{-1} 100 g^{-1} min^{-1}) was calculated from the cerebral perfusion pressure (CPP = MAP − CVP) and CBF.

Haemodynamic variables, blood-gas tensions and temperature were measured at the same intervals as CBF and 8, 16 and 24 h after surgery. In addition, the requirements for inotropic drugs were recorded.

Physiological variables between treated and untreated patients were compared with Mann–Whitney rank sum test. For statistical comparison of number of patients in defined groups, chi-square test was used. The Wilcoxon signed rank sum test was used for comparison of changes during the procedure. As this was a study primarily of CBF, power analysis was performed of possible effects on CBF and not on neurological outcome. In a previous study [23] mean CBF during CPB was 12 ml 100 g^{-1} min^{-1}. Nimodipine doubled CBF after cardiac arrest in man [11]. If CBF increased 50% with nimodipine in the present study, with SD = 4, 10 patients in each group would be sufficient for $P < 0.05$ with a power of 90%.

The neuropsychological tests were analysed with Student's *t* test, and correlation analysis for age, sex and education was performed on the differences before and after the operation. All values are mean (SEM).

TABLE II. *Patient data, cardiovascular state and operative details. AVR = Aortic valve replacement; MVR = mitral valve replacement.* *P < *0.05*

	Nimodipine (n = 18)	Placebo (n = 17)
Age (yr)	62 (2)	59 (2)
Sex (M/F)	13/5	12/5
Hypertension	1*	5*
Previous myocardial infarction	6	8
Ejection fraction (%)	64 (3)	53 (5)
AVR-MVR/CABG	8/10	6/11

RESULTS

Four patients (two nimodipine, two placebo) were excluded as it was not possible to inject xenon-133 into the right carotid artery because of non-symptomatic stenosis, leaving 35 patients (18 nimodipine, 17 placebo). There were no significant differences in patient characteristics or type of surgery between the groups, except that significantly more patients in the placebo group were hypertensive (table II). Long term calcium channel blocker treatment was stopped at least 48 h before the operation in seven patients (three nimodipine, four placebo).

There were no significant differences between the two groups in haemodynamic variables, blood-gas tensions, PCV or temperature (table III), or in durations of surgery or CPB.

The CBF values obtained before and after CPB by the i.v. method [20] (21.5 (2.1) ml 100 g^{-1} min^{-1} and 30.4 (2.2) ml 100 g^{-1} min^{-1}) were not significantly different from those obtained by the intra-arterial method [21] (22.3 (1.5) ml 100 g^{-1} min^{-1} and 30.1 (1.7) ml 100 g^{-1} min^{-1}). The results from the two methods were therefore pooled.

There were no significant differences in CBF between the nimodipine group and the placebo group at any time (fig. 2) or in CVRI. CBF increased significantly with a concomitant decrease in CVRI during hypothermic CPB in both groups and remained increased after CPB in the nimodipine group. In the placebo group, CBF was not significantly different 15 min after discontinuation of the infusion from before CPB.

There were no significant differences in the need for inotropic drugs between the two groups during weaning from CPB or during the first 24 h after operation.

Seven patients did not undergo neuro-

TABLE III. *Mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance index (SVRI), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), pH,* P_{CO_2}, P_{O_2}, PCV AND OESOPHAGEAL TEMPERATURE IN PATIENTS GIVEN NIMODIPINE (n = *18*) *(N) or placebo* (n = *17*) *(P) during and 8, 16, 24 h after operation*

Variable	After sternot. pre-CPB	During CPB			After CPB		After operation		
		0 min	15 min	45 min	Immed.	15 min	8 h	16 h	24 h
MAP (mm Hg)									
N	77 (2)	60 (3)	58 (2)	57 (3)	77 (3)	80 (2)	78 (2)	73 (2)	79 (3)
P	82 (3)	58 (3)	65 (3)	64 (4)	86 (4)	84 (4)	84 (3)	79 (2)	86 (2)
CI (litre m^2)									
N	2.1 (0.1)	2.3 (0.1)	2.2 (0.1)	2.4 (0.1)	3.2 (0.4)	2.9 (0.3)	2.3 (0.3)	2.8 (0.3)	3.2 (0.4)
P	2.5 (0.2)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.6 (0.2)	2.6 (0.3)	2.3 (0.1)	2.6 (0.1)	3.0 (0.2)
SVRI (dyn cm^{-5} m^2)									
N	2985 (273)	1968 (131)	2074 (137)	1857 (162)	1896 (237)	2220 (227)	2751 (225)	2131 (204)	2048 (213)
P	2747 (250)	1732 (103)	2150 (130)	2053 (168)	2465 (305)	2586 (354)	2967 (259)	2326 (157)	2102 (128)
CVP (mm Hg)									
N	6 (1)	3 (1)	2 (1)	3 (1)	10 (1)	10 (2)	9 (1)	9 (1)	9 (1)
P	5 (1)	3 (1)	3 (1)	2 (1)	10 (1)	10 (1)	8 (1)	8 (1)	10 (1)
PCWP (mm Hg)									
N	10 (1)	—	—	—	14 (1)	13 (1)	11 (1)	11 (1)	12 (1)
P	9 (1)	—	—	—	13 (2)	14 (1)	11 (1)	11 (1)	12 (1)
pH									
N	7.43 (0.01)	7.40 (0.01)	7.39 (0.01)	7.37 (0.01)	7.40 (0.01)	7.41 (0.01)	7.43 (0.01)	7.40 (0.01)	7.38 (0.01)
P	7.42 (0.01)	7.41 (0.01)	7.38 (0.01)	7.39 (0.01)	7.40 (0.01)	7.41 (0.01)	7.43 (0.01)	7.39 (0.01)	7.37 (0.01)
P_{CO_2} (kPa)									
N	4.6 (0.2)	4.8 (0.1)	5.3 (0.1)	5.5 (0.1)	4.8 (0.1)	4.8 (0.1)	4.9 (0.2)	5.2 (0.2)	6.1 (0.2)
P	4.5 (0.2)	4.7 (0.1)	5.1 (0.2)	5.0 (0.2)	5.0 (0.2)	4.9 (0.2)	4.7 (0.2)	5.4 (0.2)	6.6 (0.3)
P_{O_2} (kPa)									
N	22.2 (3.3)	23.9 (3.1)	30.4 (5.0)	23.9 (3.5)	29.1 (6.3)	29.1 (6.2)	23.1 (2.3)	16.1 (1.4)	14.4 (1.0)
P	23.1 (2.7)	20.2 (4.5)	23.6 (3.6)	30.8 (3.2)	32.7 (6.1)	32.7 (6.2)	27.4 (1.5)	17.8 (1.3)	16.0 (1.2)
PCV									
N	0.35 (0.01)	0.24 (0.01)	0.25 (0.01)	0.25 (0.01)	0.29 (0.01)	0.30 (0.02)	—	—	—
P	0.36 (0.01)	0.22 (0.01)	0.23 (0.01)	0.24 (0.01)	0.30 (0.01)	0.32 (0.01)	—	—	—
Temp. (°C)									
N	36.1 (0.2)	27.7 (0.4)	30.4 (0.5)	34.1 (0.9)	37.0 (0.1)	37.0 (0.1)	37.4 (0.2)	38.4 (0.2)	38.1 (0.1)
P	36.1 (0.1)	30.9 (0.7)	32.3 (0.7)	35.2 (0.9)	37.2 (0.1)	37.0 (0.1)	37.6 (0.1)	38.5 (0.1)	38.3 (0.2)

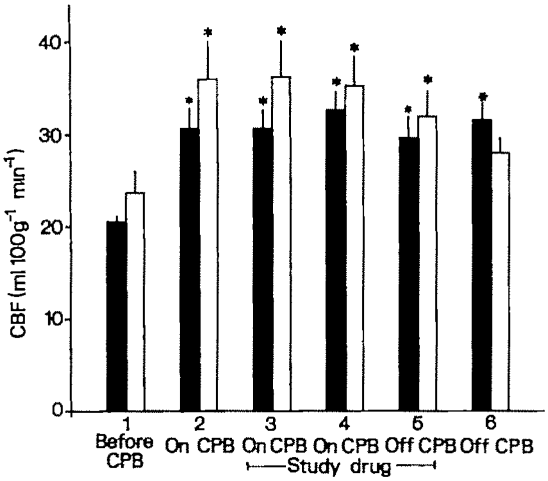

FIG. 2. Cerebral blood flow (CBF) measured before, during and after cardiopulmonary bypass (CPB) in patients treated with nimodipine (■) ($n = 18$) or placebo (□) ($n = 17$) when on CPB. *$P < 0.05$ compared with the value before CPB.

psychological testing 6 months after surgery. In the nimodipine group two died (cardiac failure, sepsis) and three declined, while in the placebo group two patients died (cardiac failure), leaving 13 in the nimodipine group (five valve replacement, eight CABG) and 15 in the placebo group (five valve replacement and 10 CABG). The first five patients were tested also within 5 days of surgery, but this was discontinued as the general physical condition of the patients influenced the test results so that it was not possible to evaluate adequately any changes.

Significant differences were found in six variables of 31 tested 6 months after surgery. Verbal fluency [15] was unchanged in the nimodipine group and decreased significantly in the placebo group. There was an improvement in the Benton visual test [16] in the nimodipine group, the results in the placebo group being unchanged. In two attention and psychomotor tests, both groups showed improvement after surgery. Two test variables for mental state were decreased after surgery, but did not show any differences between the groups.

DISCUSSION

Nimodipine 0.5 µg kg^{-1} min^{-1} did not affect CBF during or immediately after CPB in man. We have reported previously that the same dose doubled CBF in the hypoperfusion period following resuscitation from cardiac arrest in man [11]. Nimodipine has been reported also to increase CBF after regional cerebral ischaemia [10], but not in non-ischaemic areas [24, 25].

The present findings are in agreement, as there were no signs of cerebral ischaemia in our patients. The least of 975 regional values measured during hypothermic CPB was 14 ml 100 g^{-1} min^{-1}; this exceeds the values thought to be critical during hypothermic anaesthesia [26, 27].

Neuropsychological testing appears to be a sensitive index of cerebral damage. Early testing may show minor reversible changes, but such results are unreliable because of fatigue, anxiety and sleep deprivation. In the present study, the patients were tested 6 months after surgery. Those patients who underwent early postoperative testing showed reduced test scores of indeterminate cause. Performance decreased only in three of 31 tests, so we cannot conclude that there were definite signs of ischaemic damage. The separate analysis of the two groups showed a slightly better outcome for nimodipine-treated patients in terms of verbal fluency and visual retention. It may be postulated that some memory functions were preserved better in this group, but no firm conclusions can be drawn.

The values for CBF before CPB in the present study are similar to those reported by others [23, 28]. Those found during hypothermic CPB are comparable also, but the range of values is greater [29, 30]. These apparent discrepancies may be explained at least partly by variations in factors known to influence CBF, such as Pa_{CO_2}, anaesthesia, temperature, PCV and arterial pressure.

Another factor that could be important is the method used for evaluation of CBF during CPB. In earlier studies [28, 31, 32] CBF during CPB was calculated by the Height/Area (H/A) formula after injection of xenon-133 into the arterial port of the pump oxygenator. The H/A calculation requires instantaneous arrival of the tracer at the brain [33], and it is not obvious that this criterion is fulfilled when the tracer is injected in the arterial line of the pump oxygenator. The calculation of initial slope index used in the present study is independent of the input function of the tracer [21] and influenced only minimally by recirculation. The index is completed in 1 min, while the H/A measurement requires 10–15 min, and it might be difficult to keep stable all variables such as temperature, Pa_{CO_2}, PCV and cerebral perfusion pressure.

Although CBF did not change with termination of CPB, the post-CPB values were significantly greater than those before CPB, as was found by Johnsson and colleagues [29] and Feddersson and colleagues [30]. As there were no signs of ischaemia during CPB, this increase cannot be explained as post-ischaemic hyperperfusion. It seems more likely to be caused by the 15% reduction in PCV and possible changes in blood rheology.

Nimodipine 0.5 $\mu g\ kg^{-1}\ min^{-1}$ was well tolerated systemically, as there were no differences in any haemodynamic variables or in requirement for circulatory support between the nimodipine and placebo groups. Nimodipine did not affect CBF during or after CPB. Neuropsychological testing 6 months after operation suggested some benefits from treatment, but the small number of patients studied prevents firm conclusions on cerebral protective effect.

ACKNOWLEDGEMENTS

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FUNCTIONAL AND METABOLIC EFFECTS OF BUPIVACAINE AND LIGNOCAINE IN THE RAT HEART–LUNG PREPARATION

S. KASHIMOTO, M. KUME AND T. KUMAZAWA

SUMMARY

We have examined the effects of bupivacaine and lignocaine on myocardial metabolism in the rat isolated heart–lung preparation. Bupivacaine 1, 5 or 25 µg ml⁻¹ or lignocaine 4, 20 or 100 µg ml⁻¹ was administered 5 min after the start of perfusion. Both bupivacaine 25 µg ml⁻¹ and lignocaine 100 µg ml⁻¹ reduced heart rate significantly. Bupivacaine 25 µg ml⁻¹ was associated with a higher incidence of arrhythmias than the other groups. Three hearts in the bupivacaine 25 µg ml⁻¹ group ($n = 8$*) and two hearts in the lignocaine 100 µg ml⁻¹ group (*$n = 8$*) failed (zero cardiac output) at the end of the experiment. Although there were no significant differences in myocardial lactate and glycogen concentrations between groups, ATP content in the bupivacaine 25 µg ml⁻¹ and lignocaine 100 µg ml⁻¹ groups was significantly less than that in the control group. The results suggest that myocardial depression and subsequent metabolic deterioration occurred with both the high doses of local anaesthetics; these findings do not account for the apparent increased cardiotoxicity of bupivacaine.*

KEY WORDS

Anaesthetics, local: bupivacaine, lignocaine. Heart: metabolism.

In 1979, Albright suggested that bupivacaine and etidocaine are more selectively cardiodepressant than agents such as lignocaine [1]. This report led to considerable animal experimentation in an effort to clarify the mechanisms by which bupivacaine may cause cardiodepression, ventricular arrhythmias, cardiac arrest and death. Some investigators reported that the degree of cardiovascular depression is related to anaesthetic potency [2–6], while others have suggested that bupivacaine has a greater cardiovascular toxicity and a lesser margin of safety [7–11].

Many studies have assessed the cardiovascular effects of local anaesthetics. However, the direct effects of local anaesthetics on the heart are obscured by sympathetic activation caused by CNS effects [12]. Therefore, some studies have been performed in intact animals by giving the drugs into a coronary artery in order to separate CNS and cardiac effects of local anaesthetics [3, 6].

This study was designed to evaluate the functional and metabolic changes induced by bupivacaine and lignocaine in the rat isolated heart–lung preparation. This technique obviates confounding neurohumoral effects of *in vivo* studies.

MATERIALS AND METHODS

The experiment was performed in accordance with Guidelines for Animal Experiments, Yamanashi Medical College. The techniques used were identical to those used earlier [13]. Briefly, 56 male Wistar–Kyoto rats (300–320 g) were anaesthetized with pentobarbitone 50 mg kg⁻¹ i.p. Tracheotomy was performed, and intermittent positive pressure ventilation was instituted with air. The chest was opened and flooded with ice-cold saline and the heart arrested. Cannulae were inserted into the aorta and the superior (for measurement of central venous pressure) and inferior venae cavae.

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The heart–lung preparation was perfused with a solution containing red blood cells collected from another rat and Krebs Ringer bicarbonate buffer, with PCV 25 % and pH 7.4. The concentrations (mmol litre^{-1}) of the buffer constituents were: NaCl 127, KCl 5.1, $CaCl_2$ 2.2, KH_2PO_4 1.3, $MgSO_4$ 2.6, $NaHCO_3$ 15 and heparin. The perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir kept at 37 °C and returned to the inferior vena cava. In this model, no other organs except heart and lung were perfused. Cardiac output was determined by the inflow, provided the heart did not fail, and systolic arterial pressure was regulated by pneumatic resistance.

Heart rate was recorded with a bioelectric amplifier (Nihon Kohden AB-621G) and cardiac output was measured with an electromagnetic flow meter (MFV-1200). Arterial and right atrial pressures were measured with transducers (TP101T and LPU-0.1A) and carrier amplifiers (AP-621G).

All hearts were perfused initially with a cardiac output of 30 ml min^{-1} and systolic arterial pressure 80 mm Hg. Five minutes after the start of perfusion, bupivacaine 1 μg ml^{-1}, 5 μg ml^{-1} or 25 μg ml^{-1}, or lignocaine 4 μg ml^{-1}, 20 μg ml^{-1} or 100 μg ml^{-1} was added to the reservoir except in the control group. Eight animals were studied in each of the seven groups which were denoted according to the dose of local anaesthetics: B1, B5, B25, L4, L20, L100 and C. During perfusion, atrioventricular (A–V) block was defined as asynchrony of atrial and ventricular electrical activity.

Thirty minutes after the start of the study, hearts were freeze-clamped and freeze-dried for 6 days. An aliquot was extracted with perchloric acid and centrifuged at 3000 *g*. Concentrations of ATP and lactate were measured spectrophotometrically by standard techniques [14]. Another piece of freeze-dried sample was placed in 30 % potassium hydroxide and digested at 100 °C. Tissue glycogen was extracted, hydrolysed and assayed as glucose equivalents [15]. The values were expressed as μmol/g dry weight.

Statistical analysis used one-way analysis of variance followed by the Dunnett test. The incidence of A–V block, ventricular rhythm or stand still was analysed by chi-square test. A probability of $P < 0.05$ was regarded as statistically significant. The data are given as means (SD).

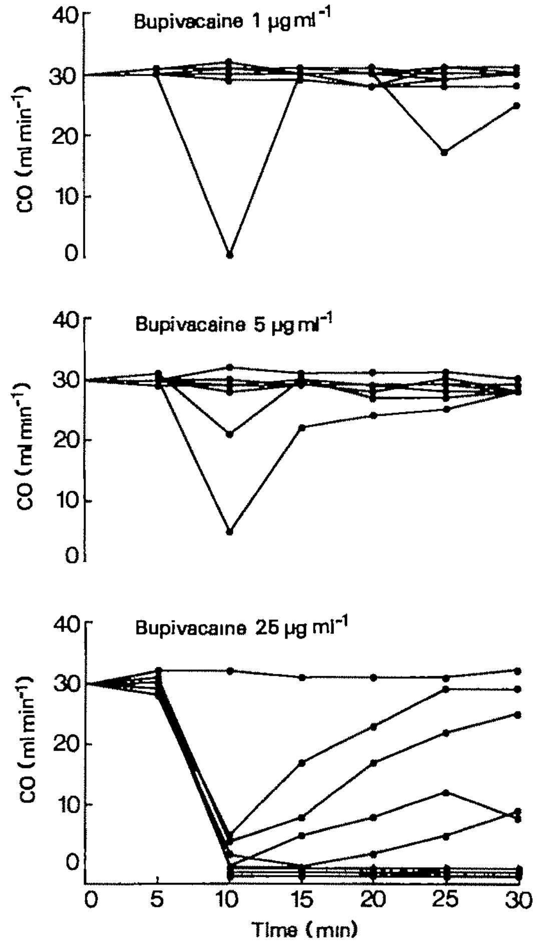

FIG. 1. Changes in cardiac output (CO) after administration of bupivacaine ($n = 8$ each group).

RESULTS

One heart in each of the B1, B5 and L20 groups failed immediately after the administration of drugs. However, they recovered at the end of the experiment. Three hearts in the B25 group and two in the L100 group failed to recover (zero cardiac output) at the end of the experiment (figs 1, 2) and are excluded from analysis of heart rate changes.

Because there was considerable variability between animals in control values of heart rate, values after administration of drug are presented as the percentage mean changes from baseline values. Heart rate decreased significantly in the B25 and L100 groups after administration of drug (table I).

The incidence of A–V block, ventricular

TABLE I. *Percentage changes in heart rate from baseline values. B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml⁻¹, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml⁻¹, respectively.* n = *8 each group except as specified.* *P < *0.05* vs *control*

	Time (min)					
Group	5	10	15	20	25	30
Control	106 (7)	108 (6)	102 (9)	100 (11)	98 (11)	94 (13)
B1	96 (8)	88 (9) (*n* = 7)	85 (7)	82 (10)	74 (18)*	75 (18)
B5	105 (8)	82 (28)*	81 (24)	80 (16)	82 (11)	81 (12)
B25	103 (12)	37 (26)* (*n* = 3)	42 (29)* (*n* = 4)	45 (26)* (*n* = 5)	45 (18)* (*n* = 5)	50 (21)* (*n* = 5)
L4	104 (6)	99 (6)	97 (9)	95 (9)	93 (9)	94 (14)
L20	114 (14)	102 (24)	88 (34)	94 (13)	95 (11)	96 (12)
L100	103 (15)	29 (14)* (*n* = 4)	40 (22)* (*n* = 6)	50 (27)* (*n* = 6)	53 (24)* (*n* = 6)	61 (21)* (*n* = 6)

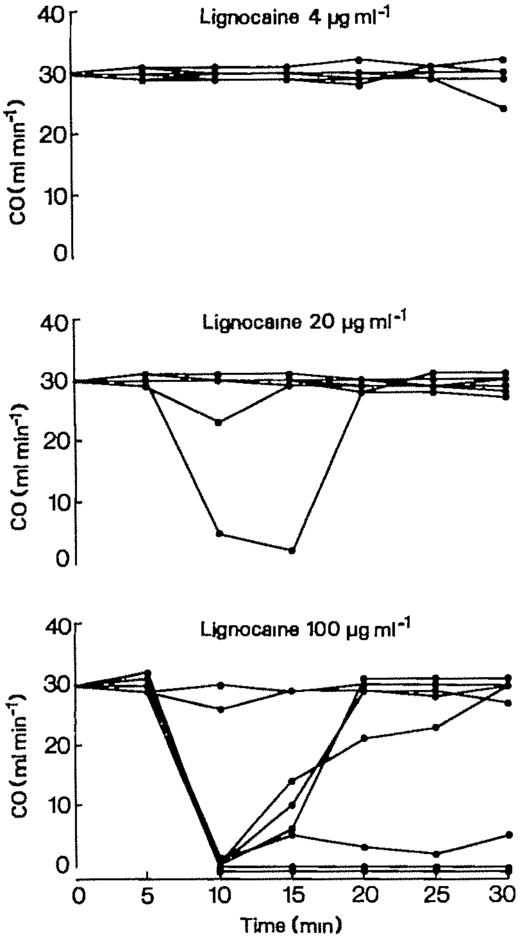

FIG. 2. Changes in cardiac output (CO) after administration of lignocaine (*n* = 8 each group).

TABLE II. *Incidence of A–V block, ventricular rhythm or cardiac arrest. B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml⁻¹, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml⁻¹.* n = *8 each group.* *P < *0.05* vs *other groups*

	Time (min)				
Group	10	15	20	25	30
B1	1	1	1	1	1
B5	2	0	1	0	0
B25	7*	7*	7*	7*	7*
L4	0	0	0	0	0
L20	1	1	0	0	0
L100	7*	6*	3	4	4

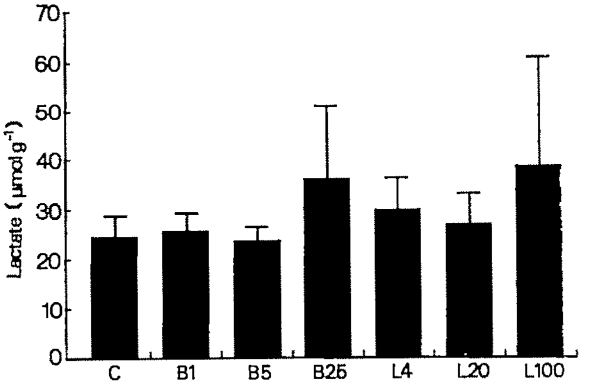

FIG. 3. Myocardial concentrations of lactate (*n* = 8 each group). C = Control; B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml⁻¹, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml⁻¹, respectively.

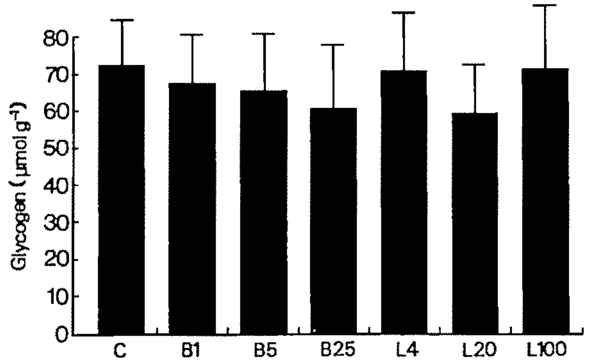

FIG. 4. Myocardial concentrations of glycogen ($n = 8$ each group). C = Control; B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml^{-1}, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml^{-1}, respectively.

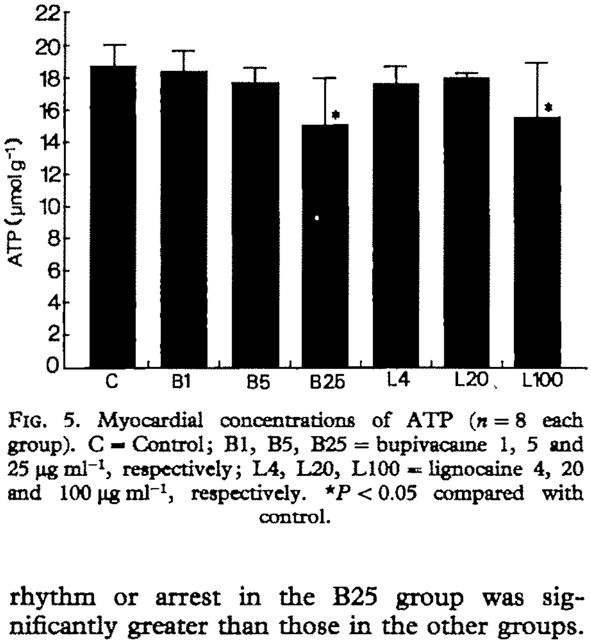

FIG. 5. Myocardial concentrations of ATP ($n = 8$ each group). C = Control; B1, B5, B25 = bupivacaine 1, 5 and 25 μg ml^{-1}, respectively; L4, L20, L100 = lignocaine 4, 20 and 100 μg ml^{-1}, respectively. *$P < 0.05$ compared with control.

rhythm or arrest in the B25 group was significantly greater than those in the other groups. However, 50% of hearts in the L100 group did not show arrhythmia 15 min after administration of drug (table II).

There were no significant differences in lactate and glycogen concentrations between groups (figs 3,4). However, ATP contents in the B25 and L100 groups were significantly less than that in the control group (fig. 5).

DISCUSSION

Bupivacaine 25 μg ml^{-1} and lignocaine 100 μg ml^{-1} depressed cardiac function markedly. However, there were almost no differences in cardiac output, heart rate changes or myocardial metabolism between equianalgesic doses of bupivacaine and lignocaine. Other investigators have reported that cardiovascular toxicity of bupivacaine is either comparable to its anaesthetic potency [2–6, 12] or greater than that of lignocaine [7–11].

In the isolated rat heart, Komai and Rusy demonstrated that the ratio between bupivacaine and lignocaine for slowing ventricular rate to 50% of control was 14:1 [7]. Tanz and colleagues [8] concluded that 3 μg ml^{-1} of unbound bupivacaine was more cardiotoxic than 30 μg ml^{-1} of unbound lignocaine in the isolated guineapig heart. Lynch [11] found a 10:1 ratio (lignocaine:bupivacaine) for equal contractile depression in isolated guineapig papillary muscle. In the isolated canine heart, the depression of contraction ratio was 8.1:1 (L:B) [16]. In an *in vivo* study, Rosen and others [10] demonstrated that bupivacaine was more cardiotoxic than lignocaine, and that in sheep this toxicity was enhanced by hypercarbia, acidosis and hypoxia. Recently, Nancarrow and colleagues [17] also have reported greater cardiotoxicity of bupivacaine compared with lignocaine in the sheep.

In contrast, Nath and colleagues [3] studied anaesthetized pigs and found dose-dependent depression of the left ventricle in the same ratio as anaesthetic potency (B:L = 4:1), although comparable prolongations of the QRS interval with bupivacaine and lignocaine were obtained at a dose ratio of 1:16. Recent studies also have reported that the degree of cardiotoxicity of local anaesthetics was related to anaesthetic potency [4–6].

This difference may result from several factors. First, bupivacaine is more likely than lignocaine to cause sodium channel block [9], A–V conduction block [7, 18] and ventricular arrhythmias [12, 16, 19–23]. These results are consistent with ours. Second, it may be attributed to species differences. For example, Kasten and Martin [24] demonstrated that sheep are more sensitive to bupivacaine than are dogs. In addition, bupivacaine is less toxic than lignocaine in mice when given i.p. [25]

Differences may result from the use of nonblood perfusion medium in the isolated preparations. However, Cronau and co-workers [26] reported that, in the working rat heart model, the acute depressant effects of bupivacaine and lignocaine on cardiac function were exerted in a potency ratio of approximately 4.59. This is similar to anaesthetic potency. Finally, it has been suggested that the CNS is the primary target organ for the toxic effects of local anaesthetics [27], and that the CNS plays a role in mediation of the cardiovascular system toxicity of local anaesthetics [28]. Heavner [22] provided evidence that the CNS effects of bupivacaine, but not lignocaine, induced ventricular arrhythmias in cats (independent of direct cardiac effects) when injected into the cerebral ventricle. However, Kotelko and others [20] observed that equivalent doses of lignocaine or bupivacaine produced similar CNS toxicity when injected rapidly i.v. in conscious sheep.

Although Eledjam and colleagues [29] suggested that inhibition of energy metabolism is a major mechanism of cardiac depression produced by bupivacaine, local anaesthetics do not exert depressant effects by influencing tissue high energy phosphate content [26]. In our study, there were no significant differences in myocardial lactate and glycogen concentrations between groups. However, ATP contents in the highest dose groups were significantly less than that in the control group. This may be a reflection of the fact that three and two hearts in the highest dose groups failed to recover at the end of the experiment, as ATP concentrations in the non-failed hearts of the B25 and L100 groups were 17.1 (2.2) and 17.4 (1.3) μmol g^{-1}, respectively. These data were not significantly different from those in the control group. From these results, we speculate that high doses of local anaesthetics may depress cardiac contractility and thereby reduce the myocardial content of ATP.

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DESFLURANE AND SEVOFLURANE: INHALATION ANAESTHETICS FOR THIS DECADE?

R. M. JONES

HISTORY AND DEVELOPMENT

It was not until the 1930s that anaesthetic agents were developed in the light of some understanding of structure–activity relationships. Probably the first to be investigated with this principle in mind was divinyl ether when, in 1930, Leake and Chen thought the compound might combine some of the advantages of diethyl ether and ethylene [4]. Previously, it had been chance observation, as much as any other factor, which brought a new compound to the attention of chemists and physicians. For instance, Arno Luckhardt first suspected that the gas ethylene might have anaesthetic properties when learning that the botanists, Crocker and Knight, had shown that it prevented carnation buds from opening [36]. The anaesthetic potential of halogens had long been known, but the particular advantages of fluorine compounds were perceived much earlier than is often appreciated. In a prophetic introduction to their studies on fluorine derivatives of chloroform, published in 1932, Harold Booth and E. May Bixby of Western Reserve University, Cleveland stated [1]: "A survey of the properties of 166 known gases suggested that the best possibility of finding a new noncombustible anesthetic gas lay in the field of organic fluoride compounds. Fluorine substitution for other halogens lowers the boiling point, increases stability, and generally decreases toxicity".

Fluorine, the halogen with the lowest atomic weight (18.998; chlorine = 35.453, bromine = 79.904 and iodine = 126.904) was first identified in 1771 by the Swedish chemist, Karl Scheele, but it was not isolated until 1886, when Henri Moissan used platinum electrodes at low temperatures to separate fluorine from hydrogen fluoride. Fluorine is very active chemically and although it forms extremely stable bonds with other elements, these are often created explosively. Thus, although it was appreciated as early as 1932 that the fluorination of compounds might produce non-combustible, stable and non-toxic anaesthetic agents, the techniques of fluorine chemistry were not advanced enough for sufficient variety of compounds to be synthesized and investigated.

The impetus to advance fluorine chemistry came from two military goals of the Second World War. First, it was found that hydrogen fluoride accelerated the catalytic alkylation of isoparaffins, which greatly enhanced the production of high octane aviation fuel. Second, uranium hexafluoride was found to be an essential intermediary in the creation of enriched uranium-235. Earl McBee of Purdue University had, from the early 1930s, a particular interest in fluorine chemistry and was involved in the basic work on fluorination which led to the successful creation of enriched uranium-235. In addition to research support from the secret Manhattan Project, McBee was also receiving support from the Mallinkrodt Company with a view to developing new fluorinated compounds with anaesthetic potential. Some 46 fluorine-containing compounds were synthesized by McBee and his associates and these were tested for anaesthetic activity by Benjamin Robbins of Vanderbilt University [47]. Although none of them proved ultimately to be suitable for use in man, several were very close in structure to what we now know as halothane, and in one compound it would have needed only the substitution of chlorine for bromine for McBee and his group to have produced the first non-combustible, potent, fluorinated anaesthetic agent and for postwar anaesthesia to have had a 10-year head start; but it was not to be, and it was left to Suckling, working at ICI's laboratory in Cheshire,

KEY WORDS

Anaesthetics, volatile. desflurane, sevoflurane.

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to synthesize halothane in 1951 [54]. Halothane was introduced into clinical practice in 1956, by Bryce-Smith and O'Brien in Oxford [2] and Johnstone in Manchester [28]. It cannot be over emphasized how much of an advance was the introduction of halothane into clinical anaesthesia. For the first time, the anaesthetist had an agent that was non-combustible, relatively non-toxic and which allowed fairly rapid and clear headed recovery. However, halothane had some drawbacks, notably its tendency to sensitize the myocardium to catecholamines, and the quest for even better agents continued.

Between 1959 and 1966, Terrell and his associates at Ohio Medical Products (now Anaquest, a division of The British Oxygen Company) synthesized more than 700 compounds in a programme intended specifically to produce a better inhalation anaesthetic agent [57]. The 347th and 469th compounds in this series were the halogenated (with fluorine and chlorine) methyl ethyl ethers, enflurane and isoflurane. Enflurane and isoflurane have proved to be excellent anaesthetic agents and in most developed countries they have largely supplanted halothane as the most commonly used inhaled anaesthetics. Even these agents, however, have some properties which render them less than ideal. Several compounds in Terrell's series were re-examined. Some of these were known to possess anaesthetic activity, but had been discarded for a variety of reasons, such as particular difficulties in synthesis or physical properties which made their vaporization difficult. One later compound in the series (the 653rd) was particularly difficult to synthesize—because of a potentially explosive step using elemental fluorine—and had a vapour pressure close to 1 atm, thus precluding its use with standard vaporizers. However, it was halogenated entirely with fluorine and because of this was predicted to have a very low solubility in blood. The increasing emphasis on day-stay surgery, and thus the necessity for rapid recovery from anaesthesia, was the impetus for renewed interest in this compound, now known as desflurane, which underwent initial evaluation at the University of California, San Francisco and has since (September 1988) undergone its first trials in man in London. It appears to be an attractive anaesthetic agent and is one of two new compounds currently undergoing clinical evaluation.

The other new compound started life in the early 1970s when Wallin, Napoli and Regan, research pharmacologists at Travenol Laboratories, Morton Grove, Illinois, were investigating a series of fluorinated isopropyl ethers. One of these, first synthesized by Regan, was identified as a potent anaesthetic agent [59, 60]. This became known as sevoflurane and, in common with desflurane, has a particularly low solubility in blood.

To what extent any new agent may find a future place in clinical anaesthesia depends on several factors which include clinical in addition to financial and commercial considerations. However, by defining the properties of a theoretically "ideal agent", a clearer picture of how our currently available drugs fall short of this ideal can emerge, and with this the known properties of sevoflurane and desflurane may be placed in perspective.

The "ideal" inhalation agent

The following properties are desirable in an inhalation anaesthetic agent [26, 30]:

(1) The compound should have inherent molecular stability and not be broken down by light, alkali or soda-lime, the latter property allowing its use in closed circuit systems. It should be stable, preferably without the addition of preservatives, and have a long shelf life permitting storage and use in a range of climatic conditions.

(2) It should not form flammable or explosive mixtures with air, oxygen or nitrous oxide.

(3) It should be reasonably potent, allowing use with high concentrations of oxygen.

(4) It should have low solubility in blood in order that induction of, and emergence from anaesthesia are rapid. This feature also allows flexibility in the adjustment of depth of anaesthesia.

(5) It should be pleasant and non-irritating to inhale, permitting smooth inhalation induction of anaesthesia.

(6) It should not undergo metabolism in the body and should be devoid of organ-specific toxic effects even when chronic low-dose exposure occurs, as in operating theatre staff.

(7) Cardiovascular and respiratory side effects should be minimal.

(8) Central nervous system effects should be readily reversible and there should be no associated stimulant activity. It should provide some degree of analgesia in addition to hypnosis.

(9) It should not undergo adverse interactions with other drugs or sensitize the heart to catecholamines.

If such a compound can be manufactured at a reasonable cost and can be delivered accurately and simply to the patient, it will be commercially attractive. Commentators have attempted occasionally to rank the various inhaled anaesthetics by ascribing some form of scoring system to individual properties and adding up the advantages and disadvantages of the specific agents; invariably this leads to the conclusion that their rank order is, in terms of overall merit, isoflurane > enflurane > halothane. However, the foundation for this type of exercise is very questionable because it is difficult, if not impossible, to ascribe an objective score to any given property in terms of relative importance. Indeed, the relative significance of a particular feature may vary from patient to patient; for example, a decrease in heart rate may be useful in one patient but undesirable in another. Nevertheless, by enumerating these ideal properties it is not difficult to conclude that the currently available agents, although satisfactory, are far removed from ideal anaesthetics.

DESFLURANE AND SEVOFLURANE

Physical characteristics

The physical characteristics of desflurane and sevoflurane are shown in table I with those of isoflurane, enflurane and halothane included for comparison.

Molecular weight. Generally, anaesthetic potency increases with increasing molecular weight [56]. In common with isoflurane, desflurane is a halogenated methyl ethyl ether. Having a fluorine atom instead of chlorine on the α-ethyl carbon, however, it has a lower molecular weight and is less potent. If, on the other hand, bromine replaces fluorine on the α-ethyl carbon, the potency of the resultant compound is significantly greater than isoflurane (CHF_2-O-CHBr-CF_3, which is the investigational anaesthetic, I-537). Thus it has been observed that potency increases about four-fold when chlorine (isoflurane) replaces fluorine (desflurane) and nearly three-fold when bromine (I-537) replaces chlorine [56]. It should be noted, however, that this general rule does not necessarily hold for structurally dissimilar compounds; thus sevoflurane, which is an isopropyl ether, rather than a methyl ethyl ether, has a greater molecular weight than both enflurane or isoflurane, but is significantly less potent than either.

Boiling point. Desflurane has a vapour pressure close to 1 atm at room temperature, boiling at 23.5 °C. In this respect it differs from other inhaled anaesthetics and it cannot be delivered using standard vaporizers. There are several theoretical methods by which desflurane may be delivered, but one that has been used safely is known as direct metering vaporization. In this method, an electrically heated vaporizer is maintained at 23–25 °C and the flowmeters are calibrated in ml min^{-1} of vapour output (in this respect, it resembles the Copper Kettle vaporizer described first in 1952 [44]).

Sevoflurane boils at 58.5 °C and has a vapour pressure of 21.33 kPa at 20 °C and 26.66 kPa at 25 °C. Its physical characteristics in this respect are therefore similar to those of other volatile

TABLE I. *Physical characteristics of the halogenated inhalation anaesthetics. *Stability decreases with increasing temperature, see text. †MAC value varies with age; values given are average ones for young to middle aged adults (see text for details of MAC determinations for desflurane and sevoflurane)*

	Desflurane	Sevoflurane	Isoflurane	Enflurane	Halothane
Molecular weight (Da)	168.036	200.053	184.491	184.491	197.381
Boiling point (°C)	23.5	58.5	48.5	56.5	50.2
Vapour pressure at 20 °C (kPa)	88.53	21.33	31.86	22.93	32.53
Partition coefficients					
Blood:gas	0.4	0.6	1.4	1.9	2.3
Olive oil:gas	19.0	53.0	91.0	96.0	224.0
Preservative	None	None	None	None	Thymol
Stability in moist soda-lime*	Stable	Unstable	Stable	Stable	Stable
MAC in oxygen†	~6.0%	~2.0%	1.2%	1.6%	0.7%

TABLE II. *Tissue:blood partition coefficients in man. (Data from [66], with permission)*

	Desflurane	Sevoflurane	Isoflurane	Halothane
Brain	1.29	1.70	1.57	1.94
Fat	27.2	47.5	44.9	51.1
Heart	1.29	1.78	1.61	1.84
Kidney	0.94	1.15	1.05	1.16
Liver	1.31	1.85	1.75	2.07
Muscle	2.02	3.13	2.92	3.38

anaesthetics and it can be delivered using standard vaporization techniques.

Partition coefficients. The blood:gas partition coefficient of desflurane is 0.42 [12]—lower even than nitrous oxide (0.46 [52])—and that of sevoflurane is 0.60 [61]. The exceptionally low solubility of both agents in blood indicates that uptake and elimination (and thus the rate of increase and decrease in brain tension) are especially rapid. This topic is discussed more fully in the ensuing section on uptake and elimination, but it should be noted that other tissue:blood partition coefficients also influence uptake and, more especially, elimination. Table II indicates the human tissue:blood partition coefficients of desflurane, sevoflurane, isoflurane and halothane determined by Yasuda, Targ and Eger [66]. It can be seen that desflurane has a lower solubility in all tissues examined than the other agents.

The oil:gas partition coefficient of desflurane is 18.7 [12] and that of sevoflurane is 53.4 [61]. It is important to define the specific oil used to determine the oil:gas partition coefficient and these values, and those noted in table I, refer to solubility in olive oil. Different values are recorded in different oils; for example, the partition coefficient of sevoflurane in corn oil is 41.6 [61]. There is a relationship between lipid solubility and potency which, until the introduction of more recent agents, was such that, with few exceptions, the product of MAC and the oil:gas partition coefficient was similar for all agents [13, 56]. Isoflurane (109), desflurane (114) and sevoflurane (106) have remarkably similar values (given in parentheses) which are appreciably lower than those of other agents (halothane 249; enflurane 258; diethyl ether 208; nitrous oxide 263 [13]). There are several ways of interpreting these observations (see the discussions in accounts by Eger [13], Halsey [25], Lynch [43] and Targ and colleagues [56]). One possibility is that general anaesthetics have a common mode of action, related to a relatively constant number of anaesthetic molecules dissolved in a hydrophobic phase (the so called "Unitary Theory"); however, a critical assessment of the literature suggests that it is difficult to escape the conclusion that the precise mechanism of action of anaesthetics at molecular level might vary according to the specific anaesthetic in question (this might be termed a modified or "Soft Unitary Theory"). This topic is discussed further in a later section.

Stability in soda-lime. The extent to which inhaled anaesthetics are absorbed (or degraded) by soda-lime is important when their use in low flow systems is desirable; the more expensive an agent the more important this is as a consideration. It seems likely that all anaesthetics are both absorbed and degraded to some degree at least, but that the absolute (i.e. total amount "disappearing" during the passage through soda-lime) in addition to relative (proportion absorbed compared with the proportion degraded) extent of these processes varies from agent to agent. This is important because degradation by soda-lime is related to molecular stability and unstable anaesthetics may degrade to toxic compounds both *in vitro* [51] and *in vivo* [5] (the consequences of absorption alone are mainly economic). Two generalizations can be made. First, stability decreases with increasing temperature [17, 53]; second, dry soda-lime absorbs more anaesthetic than does moist soda-lime [23, 24]. The overall stability appears to be: desflurane > isoflurane > halothane > sevoflurane [17, 53]. Desflurane seems to be very resistant to degradation—an observation in keeping with its overall molecular stability—whereas sevoflurane appears to be unstable to a degree that makes its use with soda-lime questionable. The precise extent to which sevoflurane is absorbed, rather than degraded, is open to some doubt [53, 61] and further work will need to be done before a definite conclusion can be reached. However, current evidence indicates that it disappears into soda-lime and does so in appreciable quantities at higher temperatures. For example, Strum, Johnson and Eger [53] reported that, at 22 °C, soda-lime degraded 6.5% of the sevoflurane per hour and that the rate increased by 1.6% per hour per degree increase in temperature, reaching 57.4% degradation per hour at 54 °C. In contrast, isoflurane did not

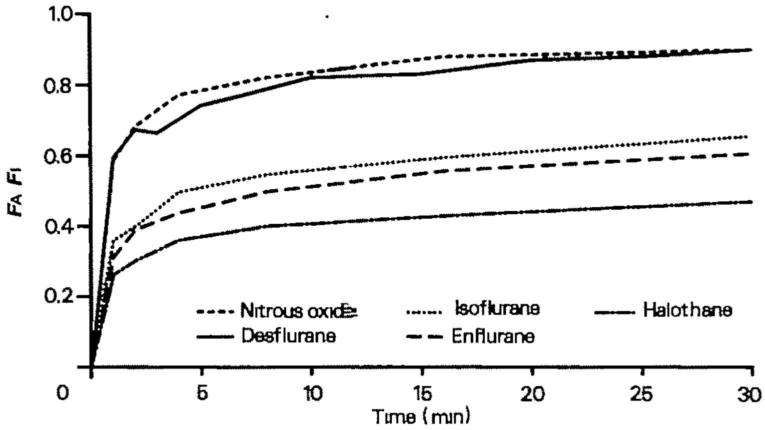

FIG. 1. Comparison of uptake of inhaled anaesthetics: rate of increase in alveolar concentration (*F*A) with respect to inspired concentration (*F*I) for nitrous oxide, desflurane, isoflurane, enflurane and halothane. (Redrawn with permission using data from Munson and colleagues [45] for nitrous oxide, halothane and enflurane; Cromwell and colleagues [8] for isoflurane; Jones and colleagues [31] for desflurane.)

degrade significantly at any temperature and halothane did not degrade at 22 °C but did so slightly at 54 °C (2.2% h^{-1}). Baralyme, an alternative to soda-lime which does not contain silica, has been shown to degrade sevoflurane to an even greater degree than soda-lime at higher temperatures [55].

Potency. The MAC of sevoflurane has been found to be 1.71 (SE 0.07)% in a study from Japan [34] and 2.05 (0.08)% in a study from North America [49]. Apart from some methodological differences between the two studies, it is likely that the potency of an agent does differ slightly in patients with different genetic backgrounds. The MAC of desflurane has been found to be 6.0 (0.90)% in surgical patients in North America [46]. Desflurane is thus significantly less potent than other inhaled anaesthetics, but is sufficiently potent to be used with high (≥90%) concentrations of oxygen. As it is stable in soda-lime, it will be a suitable agent to use in low flow anaesthetic systems.

Uptake and elimination

The low solubility of desflurane and sevoflurane in blood indicates that the rate of increase in alveolar (and thus brain) concentrations with respect to inspired concentration should be rapid, as should the decrease in alveolar concentration after discontinuation of the administration of the agent. Induction of, and recovery from, anaesthesia with these agents should thus be more rapid than with other halogenated anaesthetics. Of course, with increasing elapsed time after starting administration, the influence of solubility in other tissues, especially those of the vessel-rich group, becomes of increasing importance and in this respect the lower solubility of desflurane (in all tissues thus far studied) indicates that the cerebral concentration of this agent follows most closely that of inspired concentration. These predictions have been shown to be fulfilled in the case of desflurane. In volunteers the ratio of alveolar to inspired concentration after 10 min of exposure to desflurane was 0.82 [31]. Elimination was similarly rapid; after about 1 MAC-h exposure to desflurane the alveolar concentration, relative to the last concentration during administration of anaesthetic was 0.11 after only 10 min and volunteers awoke in 2.7 (SD 1.2) min [31]. In this respect desflurane is similar to nitrous oxide; figures 1 and 2 compare the rates of uptake and elimination of desflurane, nitrous oxide, isoflurane, enflurane and halothane. A comparison of the slopes for desflurane and nitrous oxide during elimination, as opposed to uptake, graphically demonstrates the influence of the solubility in tissues other than blood.

The rate of increase in alveolar concentration of sevoflurane has been studied in the dog [35] and has been shown to be significantly more rapid than that of isoflurane or halothane. This study did not report the elimination of the anaesthetics.

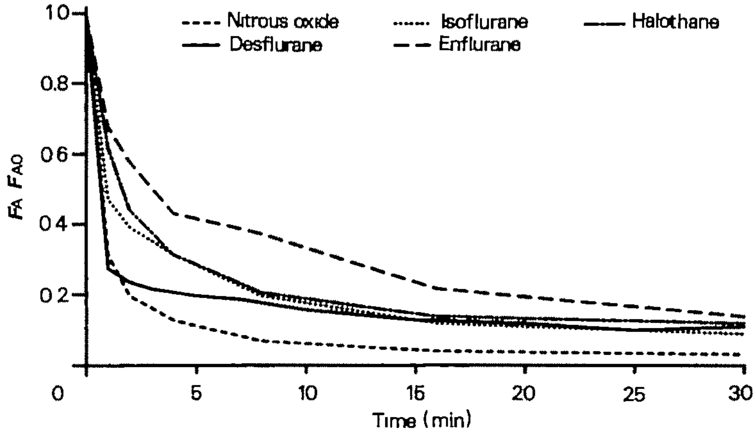

FIG. 2. Comparison of elimination of inhaled anaesthetics: rate of decrease in alveolar concentration (*F*A) with respect to the last alveolar concentration (*F*AO) during administration of the agent. (Redrawn using the same sources as in figure 1.)

The greater tissue solubility of sevoflurane, compared with desflurane, suggests that cerebral concentration is less well correlated with inspired concentration using this agent. This suggests that altering the depth of anaesthesia during surgery to meet the changing demands of the surgical stimulus is accomplished most readily with desflurane.

Cardiorespiratory effects

The respiratory effects of all potent inhaled anaesthetics are similar in that they cause a dose-related depression of respiration as indicated by an increase in arterial carbon dioxide tension [11, 18, 29, 38]. This is usually accompanied by an increase in the frequency of ventilation, with overall minute volume remaining unchanged. In addition, the ventilatory response to both hypoxia [11, 37] and carbon dioxide [11, 58] is depressed. Sevoflurane and desflurane appear to have effects very similar to those of other agents. Thus in volunteers both agents at about 1 MAC concentration cause a moderate increase (approximately 20%) in arterial or end-tidal carbon dioxide tension, accompanied by an increase in frequency of ventilation and very little change in minute volume [27, 32]. As yet there are no published data on their influence on bronchomotor tone, but it would be surprising if the agents differed from others in this respect (i.e. tone is decreased). The trend in favour of mechanical ventilation implies that patients are required less often to breathe spontaneously and the respiratory depression associated with all potent inhaled anaesthetics is becoming less important.

The cardiovascular effects of desflurane and sevoflurane appear similar to, but not necessarily indistinguishable from those of isoflurane. In volunteer studies both agents caused a decrease in systemic arterial pressure, diastolic more than systolic, with little overall influence on heart rate [27, 32]. Neither agent appears to sensitize the myocardium to the effect of catecholamines [10, 32, 62] and in this respect they resemble isoflurane more than any other agent [29]. More invasive studies have been carried out in animals. Sevoflurane causes a dose-related decrease in mean arterial pressure and cardiac contractility (as determined by changes in dP/dt) in acutely instrumented newborn piglets [9] and in chronically instrumented dogs [64]. In the latter study there was little effect on coronary blood flow, but renal blood flow decreased significantly. Studies in animals with desflurane have indicated that this agent also decreases mean arterial pressure and cardiac contractility in a dose-dependent manner [63]. There has been a preliminary report in volunteers that, although desflurane caused a decrease in arterial pressure and cardiac output at lighter levels of anaesthesia, at deeper levels these variables approached or exceeded their baseline values [3]. Although this published abstract presents the results from only three volunteers, and nitrous oxide was administered in conjunction with desflurane, the authors suggest that desflurane and nitrous oxide might cause activation of β-adrenergic activity in a manner similar to that seen with fluroxene or diethyl ether.

Further work must be carried out with these new agents before a clearer picture of their specific cardiovascular effects emerges, but preliminary evidence suggests that each will prove to have a unique cardiovascular profile.

Hepatorenal effects and biotransformation

There is a major difference between the molecular stability of desflurane and that of sevoflurane; desflurane is a remarkably stable molecule, whilst sevoflurane is not. This has already been mentioned when considering their relative stability in soda-lime. An inherently stable molecule, especially one that is poorly soluble in tissues, suggests that biotransformation should be minimal, and this in turn has implications for the toxic potential of the agent. After about 1 MAC-h exposure to desflurane, mean inorganic fluoride concentration did not exceed the control value (0.79 μmol litre^{-1}) at any time (patients were followed up for 1 week) [33]. This compares with a plasma concentration after about 1 MAC-h exposure to sevoflurane of 22.1 μmol litre^{-1} [27]. (The fluoride concentrations seen after sevoflurane anaesthesia appear to be similar to those seen after enflurane anaesthesia in terms of MAC-h exposure [unpublished data of the author].) Other studies have indicated the molecular stability and lack of biotransformation of desflurane. Koblin and his colleagues [39] have studied the biotransformation of methoxyflurane, halothane, isoflurane and desflurane in rats pretreated with phenobarbitone (to cause enzyme induction) in a series of controlled experiments. There were up to 1000-fold increases in plasma and urinary inorganic fluoride ion and urinary organic fluoride concentrations in rats exposed to halothane and methoxyflurane, whereas isoflurane caused a measurable but smaller increase and the concentrations of fluoride after desflurane were virtually indistinguishable from those of control animals. Similarly, in swine exposed to approximately 5.5 MAC-h of isoflurane or desflurane, plasma concentrations of fluoride ion were three times greater than control values immediately after and at 4 h after exposure to isoflurane, whereas there was no detectable increase immediately after anaesthesia with desflurane and only a 17% increase after 4 h [40].

The biotransformation of sevoflurane, in terms of peak plasma concentration of fluoride ion, has also been studied in animals [41, 61]. Concentrations in excess of 10 μmol litre^{-1} have been reported in rats [6] and, in guineapigs [41], concentrations approaching nephrotoxic values were found (42 μmol litre^{-1}; the nephrotoxic value is accepted generally as being approximately 50 μmol litre^{-1} [29]). In the last study there was biochemical and histological evidence of sevoflurane-induced hepatotoxicity. The authors suggested that hepatotoxicity was related to a decrease in hepatic blood flow. However, Wouters and colleagues [65] reported that hepatic arterial blood flow increased in dogs exposed to 1.2 and 2.0 MAC sevoflurane. The precise role of altered hepatic blood flow in the genesis of hepatotoxicity remains unclear, and no gross change in liver function was reported by Holaday and Smith when they carried out the first volunteer trials with sevoflurane [27]. However, Franks and colleagues have studied liver function in terms of the synthesis of the hepatic proteins fibrinogen, transferrin and albumin in an *in vitro* rat model [19]. They demonstrated that sevoflurane decreased synthesis of all proteins at clinically relevant concentrations (albumin 68.3%; fibrinogen 67.7%; transferrin 62.3%) and that, with the exception of the effect of enflurane on albumin synthesis (decreased by 71.4%), this was greater with sevoflurane than with any other agent tested.

Although there is some evidence that sevoflurane decreases renal blood flow and that moderate exposure results in plasma inorganic fluoride concentrations which may approach nephrotoxic values, there has been no evidence of gross changes in renal function in either animals [6, 7] or man [27]. However, in these studies renal function was assessed by relatively simple tests, such as plasma creatinine concentration, urinary volume and concentrating ability; more sensitive tests of tubular function, such as measurement of urinary retinol binding protein (RBP) or β-N-acetyl glucosaminidase (NAG) were not performed.

The physical stability of desflurane suggests that organ-specific toxicity with this agent will prove to be minimal or absent. Preliminary work has supported this contention. Thus in volunteer studies no alteration in liver or renal function (including changes in urinary RBP or NAG [33]) could be determined. This agent has been tested more severely in animals. Eger and his colleagues subjected rats to six 2-h exposures to 1.6 MAC isoflurane or desflurane in a controlled study and reported that no tissue damage attributable to either anaesthetic occurred, nor was weight gain affected [14]. This lack of toxicity extended to an enzyme-induced hypoxic rat model

[15]. The animals were pretreated with phenobarbitone and exposed to 12% oxygen and no anaesthetic (control) or to 1.2 MAC halothane, isoflurane or desflurane. Liver, kidney and lung specimens were examined after exposure. Pulmonary and renal damage was not evident in any of the groups, but the livers of all rats exposed to halothane had marked swelling and centrilobular necrosis, whereas isoflurane produced only slight injury. No damage was discernible in the control or desflurane groups. Current evidence, therefore, indicates that desflurane is metabolized significantly less than other anaesthetics and that this is associated with a marked absence of organ-specific toxic effects.

Environmental issues

With an atmospheric lifetime of about 150 years [50], nitrous oxide is probably the most environmentally destructive of our anaesthetics in terms of effects on the ozone layer. It can photodissociate or react with atomic oxygen in the stratosphere to produce nitric oxide, which significantly contributes to stratospheric ozone destruction and is also a significant "greenhouse gas", reflecting heat energy back to the surface of the earth [42]. Chlorine-containing anaesthetics, such as halothane, enflurane and isoflurane, may also be more destructive than the newer agents which are halogenated entirely with fluorine. Both chlorine- and fluorine-containing hydrocarbons are capable of photolysis, but it is known that atomic fluorine has an ozone depleting potential approximately 0.001% that of chlorine [42, 48]. Although the relative contribution of chlorine-containing anaesthetics to the destruction of the ozone layer has been calculated at only a fraction of 1% [42], the use of low flow absorption breathing systems coupled with the use of anaesthetics that are entirely fluorinated will be not only economic but also environmentally responsible.

FUTURE DEVELOPMENTS

It was stated at the start of this brief review that it was not until the 1930s that anaesthetics were developed in the light of some understanding of structure–activity relationships. However, the fact that, even in recent times, desflurane was the 653rd compound of a series studied for anaesthetic activity indicates that the discovery of new agents is still largely a matter of trial and error. Present evidence suggests that desflurane may approach the ideal more closely than any other inhaled anaesthetic. Although it has very low solubility in blood and other tissues, it still has some undesirable side effects (particularly cardiorespiratory). Anaesthetics with fewer side effects will be more likely to be developed when the site or sites of action of anaesthetics at molecular level are more fully understood. Compounds can then be designed specifically to act at the site involved and with this specificity should evolve anaesthetic agents with fewer unwanted effects. Thus, the "molecules to man" approach in medical research is no better demonstrated than in the quest for safer anaesthetic agents.

However, it remains controversial even where the primary target sites of general anaesthetics lie; are they proteins or lipids [16, 20, 25]? As previously pointed out, it has been appreciated since the early 1890s that there is a correlation between lipid solubility and potency and this might be the reason why particular attention has been paid to lipids in the past. More recently, attention has been paid to proteins, particularly hydrophobic pockets on proteins [22]. Work by Franks and Lieb using light emitting luciferase protein enzymes of the firefly has demonstrated that a pure soluble protein can not only bind to, but can be inhibited by, a wide range of anaesthetics at concentrations which are essentially identical to those which cause anaesthesia [21]. The correlation is so good that plotting the ED_{50} concentrations for inhibiting firefly luciferase activity against the ED_{50} concentrations for anaesthesia in populations of various animals results in a straight line; that is to say, as Franks and Lieb pointed out, the early observations of Meyer and Overton can be interpreted just as reasonably in terms of anaesthetics binding to proteins as of anaesthetics dissolving in lipids [22].

Whatever the precise site (or sites) of action of inhaled anaesthetic agents within the central nervous system proves to be—and ultimate targets are probably ion channels in nerve membranes, influenced by proteins, lipids or both—the development of truly "clean" anaesthetic agents must await identification of those sites. This is very likely to occur during the next decade and "designer drugs" based on this knowledge should be within our grasp. These, therefore, are drugs for the next millenium. For this decade we have the prospect of desflurane, and perhaps sevoflurane, being available for clinical use. Based on current evidence, can the rhetorical question posed in the title of this brief review be answered? Are desflurane or sevoflurane sufficiently nearer the ideal for them eventually to supplant enflurane and isoflurane? The question can be answered only in part. All initial evidence concerning desflurane is that this will prove to be an agent with certain properties that are a distinct improvement on those of existing anaesthetic agents. The low solubility in blood and high molecular stability are a particularly welcome combination; however, the drug is not easy to synthesize and requires a modification of our present equipment for safe delivery to the patient. The latter considerations suggest that it will be most appropriately administered using low-flow absorber systems—an environmentally responsible mode of administration for which it is entirely suitable. Sevoflurane shares with desflurane a low solubility in blood, but is not a stable molecule and there are doubts if it may be used in circle absorber systems; however, it can be used with conventional methods of vaporization and this may give it a commercial advantage. Despite a longer history, it has not been studied systematically to the same extent as desflurane. Further work needs to be performed with both agents before their likely place in anaesthetic practice can be stated with some confidence. In the case of desflurane, however, a major advance in anaesthesia may be in the offing.

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EFFECT OF ADRENALINE ON PLASMA CONCENTRATIONS OF BUPIVACAINE FOLLOWING INTRA-ARTICULAR INJECTION OF BUPIVACAINE FOR KNEE ARTHROSCOPY

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SUMMARY

We administered 0.5% bupivacaine 30 ml either with or without adrenaline 5 μg ml⁻¹ randomly to 16 healthy outpatients, to determine the efficacy of local and intra-articular local anaesthesia for knee arthroscopy and whether or not adrenaline should be added to intra-articular bupivacaine. Bupivacaine concentrations were measured in plasma obtained 15, 30, 45 and 60 min after intra-articular injection. Patients receiving bupivacaine with adrenaline had significantly smaller plasma concentrations of bupivacaine at all times than did patients receiving plain bupivacaine. The maximal concentrations of bupivacaine in the plain group (median 515 ng ml⁻¹, range 46–875 ng ml⁻¹) were greater than those in the adrenaline group (median 33 ng ml⁻¹, range 7–125 ng ml⁻¹) (P = 0.001). All patients found the anaesthetic satisfactory. We conclude that intra-articular/local anaesthesia is satisfactory for outpatient arthroscopic surgery, and that adrenaline should probably be added to bupivacaine before intra-articular injection.

KEY WORDS

Anaesthetics, local: bupivacaine, plasma concentrations. Pharmacokinetics: bupivacaine, intra-articular injection.

Diagnostic arthroscopy of the knee is undertaken usually with general or conduction anaesthesia. During the past 3 years, we have developed an intra-articular local anaesthetic technique for arthroscopy which permits ambulation and early discharge. This report describes both our technique of anaesthesia and the effect of adrenaline on plasma concentrations of bupivacaine following intra-articular injection.

METHODS AND RESULTS

Following review and approval of our study by our Clinical Research Practices Committee, we obtained informed consent from 16 healthy patients of both sexes undergoing outpatient diagnostic arthroscopy of the knee. Patients were allocated randomly to intra-articular injection of 0.5% bupivacaine either with ($n = 9$) or without ($n = 7$) adrenaline 5 μg ml⁻¹. The adrenaline group included six males and three females (median age 46 yr (range 21–84 yr); median weight 75 kg (range 50–105 kg)). The plain group included six males and one female (median age 31 yr (range 27–58 yr); median weight 80 kg (range 49–120 kg)).

Following preparation of the skin with povidone-iodine, 1% lignocaine with adrenaline 5 μg ml⁻¹ was injected s.c. 1–2 cm from the superolateral, inferolateral, and inferomedial margins of the patella using a 25-gauge needle. Using a total of no more than 20 ml (200 mg) of lignocaine, each weal was expanded to achieve cutaneous anaesthesia of the three arthroscopic ports. With the knee flexed approximately 10°, 0.5% bupivacaine 30 ml was injected slowly (over approximately 3 min) into the joint space through an 18-gauge needle inserted at the superolateral aspect of the patella. Negative aspiration (or, in some cases, aspiration of joint fluid), ease of injection and palpable distension of the joint space

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by the local anaesthetic confirmed correct needle placement. Surgery began 25–30 min later. Arthroscopy was performed without a tourniquet using the technique described by McGinty [1]. Any bupivacaine remaining in the joint space was flushed out rapidly by Hartmann's solution injected to distend the joint space.

Venous blood samples were collected 15, 30, 45 and 60 min following intra-articular injection. Samples were aspirated into citrated vacuum tubes and cooled immediately in an ice bath. Following centrifugation, the samples were subjected to gas chromatographic/mass spectrographic analysis for measurement of plasma concentrations of bupivacaine.

Numerical data are presented as means (SEM) or as medians and ranges. Bupivacaine concentrations were compared using multivariate analysis of variance for repeated measures. Fisher's exact test and Wilcoxon's rank sum test suggested that the two groups were similar in age, weight and height.

The anaesthetic was successful in every case. The arthroscopic procedure required a median time of 50 min (range 25–105 min). Patients were sedated with a median dose of fentanyl 100 µg i.v. (range 0–150 µg) and with a median dose of midazolam 3 mg i.v. (range 0–9 mg). The usual indication for sedation was excessive anxiety before operation. Patients who received fentanyl, midazolam or both typically received approximately equal doses before and after the block. Monitoring consisted of ECG (lead II), non-invasive arterial pressure, and finger pulse oximetry. Patients were discharged from our unit following a median 32.5 min recovery time (range 15–85 min).

The patients receiving bupivacaine with adrenaline demonstrated significantly ($P < 0.002$) smaller concentrations of plasma bupivacaine overall, and at all individual time points ($P \leqslant 0.01$ in every case), than patients receiving plain bupivacaine (fig. 1). Moreover, the maximal concentrations of bupivacaine achieved in each patient were less in the adrenaline group (median 33 ng ml^{-1}, range 7–125 ng ml^{-1}) than in the plain group (median 515 ng ml^{-1}, range 46–875 ng ml^{-1}) ($P = 0.001$). No patient in either group had a bupivacaine concentration greater than 1 µg ml^{-1}, the value at which toxicity has been reported [2]. There were no signs of toxic reactions to local anaesthetic or adrenaline.

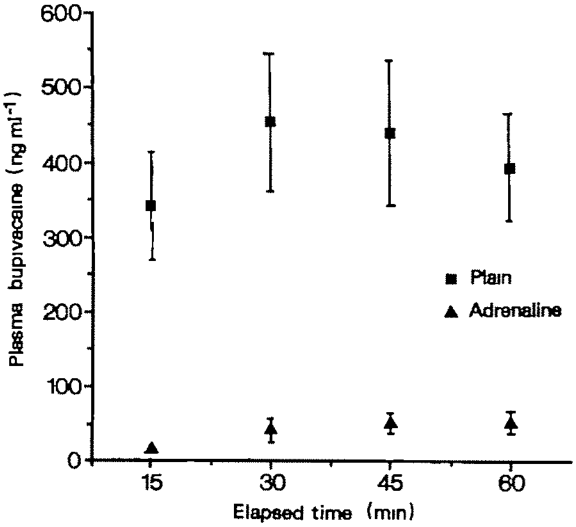

FIG. 1. Effect of adrenaline on plasma concentrations of bupivacaine following injection into the knee joint (means, SEM). Differences between groups are significant overall ($P < 0.002$) and at all time points ($P < 0.01$).

After operation, all patients were questioned by telephone on their response to the anaesthetic. All indicated that they would request the same anaesthetic if they were to require another arthroscopic procedure.

COMMENT

Our intra-articular/field block anaesthetic appears to be simple and acceptable to patients undergoing outpatient arthroscopy of the knee. As bupivacaine is chosen most often for cutaneous (in addition to intra-articular) injection, we believe that adrenaline should be added to bupivacaine when our technique is used. As the ventilatory response to sedative medication (the fentanyl and midazolam used for most of our patients) is unpredictable, we recommend that arterial oxygen saturation be monitored whenever this technique is used.

Previous reports of plasma concentrations of local anaesthetic following intra-articular injections have included a wide variety of dosing regimens [3–6]. However, none has reported bupivacaine concentrations when bupivacaine was used as the primary anaesthetic. Variations in technique may influence systemic absorption of intra-articularly injected local anaesthetics sufficiently to alter the safe range of doses. Nonetheless, both the absolute values and variability of our plasma concentrations of bupivacaine were similar to those reported by Katz and colleagues [6].

In conclusion, we believe that this local anaesthetic technique provides patient satisfaction, with minimal postoperative recovery for patients undergoing diagnostic arthroscopy of the knee. The marked reduction in peak plasma concentrations of bupivacaine produced by the addition of adrenaline may allow safe administration of bupivacaine for cutaneous anaesthesia.

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INFLUENCE OF HALOTHANE ON THE TRAIN-OF-FOUR FADE AFTER ATRACURIUM IN CHILDREN

B. WOLOSZCZUK-GEBICKA

SUMMARY

The influence of halothane was studied on train-of-four fade during spontaneous recovery from neuromuscular block produced by atracurium in 42 children undergoing routine surgical procedures under general anaesthesia. The ulnar nerve was stimulated at the wrist, and compound electromyographic responses were recorded from the adductor pollicis brevis, using a Relaxograph. One group of children was anaesthetized with nitrous oxide and 1% halothane (end-tidal concentration) in oxygen; in the other group nitrous oxide and fentanyl in oxygen was used (control group). Halothane was found to increase the train-of-four fade during the recovery phase compared with control. It is possible that presynaptic and postsynaptic cholinoceptors differ in their sensitivity to the depressant action of halothane.

KEY WORDS

Anaesthesia · paediatric. Neuromuscular transmission · train-of-four fade. Neuromuscular relaxants atracurium

It has been shown recently that muscle relaxation produced by volatile anaesthetic agents is caused by action on the neuromuscular junction [1].

There is evidence that atracurium impairs neuromuscular transmission at presynaptic and at postsynaptic sites at the motor end-plate [2, 3]. Bowman suggested that single twitch depression and train-of-four (TOF) fade are separate effects of neuromuscular blocking drugs, the former being a result of postjunctional block, and the latter resulting mainly from action at the prejunctional receptors [4].

This study was designed to investigate the effect of halothane on TOF fade produced by atracurium.

METHODS AND RESULTS

After approval was given by the local Ethics Committee, 42 children, ASA physical status I and II, requiring muscle relaxation for surgical procedures were studied. All were free from neuromuscular, renal and hepatic disease; none was taking drugs known to interfere with neuromuscular transmission. Children in group I ($n = 19$; age 5.2 (SD 1.3) yr, weight 18.1 (4.2) kg) were anaesthetized with 60% nitrous oxide and halothane in oxygen and those in group II (control group: $n = 23$; age 6.0 (3.4) yr; weight 21.1 (7.8) kg) were anaesthetized with 60% nitrous oxide and fentanyl in oxygen.

Premedication consisted of atropine 0.02 mg kg^{-1} and pethidine 1 mg kg^{-1}, given i.m. 30 min before induction of anaesthesia. In the first group, anaesthesia was induced and maintained with 60% nitrous oxide and 1% halothane (end-tidal concentration, measured using Servo-gas monitor, Siemens–Elema) in oxygen. In the control group, anaesthesia was induced using thiopentone 5 mg kg^{-1} i.v. and maintained with 60% nitrous oxide and fentanyl 4–6 µg kg^{-1} in oxygen, as required. Atracurium (bolus or two incremental doses) was given after induction of anaesthesia to produce 95–100% block of neuromuscular transmission and facilitate tracheal intubation. The lungs were ventilated artificially to an end-tidal $P\text{CO}_2$ of 4.7–6 kPa (Datex Capnograph).

Spontaneous recovery of neuromuscular transmission was allowed.

Neuromuscular transmission was studied using a Relaxograph (Datex). The ulnar nerve was stimulated at the wrist via two surface electrodes. Train-of-four stimulation, 2 Hz for 2 s, every

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20 s, was applied. The compound electromyogram was measured from the adductor pollicis brevis via two surface electrodes. The ratio between the height of the first twitch (T1) before and after atracurium (T1:control (%)) and the ratio between the height of the fourth and the first twitch in the same train (TOF ratio) were analysed.

Comparison of TOF fade was made during nitrous oxide and halothane in oxygen and during nitrous oxide and fentanyl in oxygen anaesthesia. The T1:control and TOF ratios during spontaneous recovery, expressed as percent of appropriate baseline values, were transformed to logit values, which were plotted subsequently against natural logarithm of time. The slope of the line was calculated by regression analysis, and the difference of the regression coefficient was compared, using standard tests for statistical significance.

When the degree of fade was compared at a T1:control of 25%, the TOF ratio in children in the halothane group did not differ from that in the control group (11% *vs* 14%); at a T1:control of 50%, the TOF ratio was 21% in the halothane group and 35% in control subjects; at a T1:control of 75%, the TOF ratios were 44% and 63%, respectively. The regression coefficient for the TOF ratio during the recovery phase in the halothane group was significantly different from control ($P < 0.05$).

COMMENT

After a bolus dose of a neuromuscular blocking agent, and after a redistribution phase of four to five half-lives, the elimination phase of the drug begins, when pseudoequilibrium exists between plasma and tissue concentrations. Under these circumstances, there is a constant and reliable relationship between the absolute values of T1:control and TOF ratios.

Halothane was found to influence this relationship; the TOF ratio during anaesthesia with nitrous oxide and 1% halothane in oxygen was significantly smaller than that of controls. There is recent evidence [3] that the site for synergism of volatile anaesthetics and non-depolarizing neuromuscular blocking agents is at a receptor (or receptors) within the neuromuscular junction.

Although there is no proof, it is possible that a site other than postsynaptic (possibly presynaptic) may be responsible for fade during high frequency stimulation (tetanic or train-of-four). Bowman suggested that the prejunction receptors are isoreceptors of postsynaptic cholinoceptors which serve to mediate mobilization of reserve transmitter to the readily releasable pool within the axoplasm [4]. It is believed that these prejunctional receptors function as a positive feedback control system that maintains availability of acetylcholine when demand is high. Fade during high frequency stimulation may represent the action of neuromuscular blocking drugs at sites other than postsynaptic receptors, probably prejunctional cholinoceptors. The results of this study suggest that this receptor may be influenced also by halothane.

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AN UNUSUAL COMPLICATION OF BRACHIAL PLEXUS SHEATH CANNULATION

K. W. PATTERSON AND P. SCANLON

SUMMARY

A 20-gauge cannula placed via an interscalene approach in the left brachial plexus sheath of a healthy 18-yr-old male was used inadvertently for injection of 20 ml of antibiotic solution, despite clear labelling of the cannula and painful protest from the patient. The patient suffered no neurological sequelae. The treatment, possible causes and steps to avoid similar incidents are described.

KEY WORDS

Anaesthetic techniques, regional· continuous brachial plexus block. Complications: inadvertent antibiotic injection.

In recent years at our hospital, traumatic amputations involving the upper limbs have been undertaken using a combination of regional and general anaesthetic techniques. One of the recognized rare complications of this technique is inappropriate injection of solutions other than local anaesthetics [1].

We describe the injection of flucloxacillin 10 ml around the brachial plexus in a patient who had a 20-gauge i.v. cannula left in the brachial plexus sheath after surgery.

CASE REPORT

An 18-yr-old male was transferred to the plastic surgery unit following traumatic amputation of his left thumb. The injury was of a rotation avulsion type, with complete amputation of the thumb and a vertical fracture through the proximal phalanx. The accident happened 8 h before transfer and during that time there was warm ischaemia for 3 h and cold ischaemia for 5 h. After assessment, the patient was transferred to the operating theatre for re-implantation. In order to improve blood flow to the limb and for post-operative pain relief, a 20-gauge cannula was inserted via an interscalene approach into the left brachial plexus sheath with the aid of a peripheral nerve stimulator. Forty millilitre of 0.5% bupivacaine with adrenaline 1:400000 was injected. General anaesthesia was induced with thiopentone and neuromuscular block produced with suxamethonium followed by pancuronium; the lungs were ventilated with 60% nitrous oxide and isoflurane in oxygen. Surgery lasted 5 h and was uneventful; the thumb was re-implanted successfully and revascularized with a vein graft from the forearm. Flucloxacillin 500 mg i.v. was commenced at 6-h intervals. Before the patient was transferred to the ward, the brachial plexus cannula was labelled clearly (fig. 1).

The following day, the patient was returned to theatre for exploration, as the thumb had become cyanosed. The arm was anaesthetized with bupi-

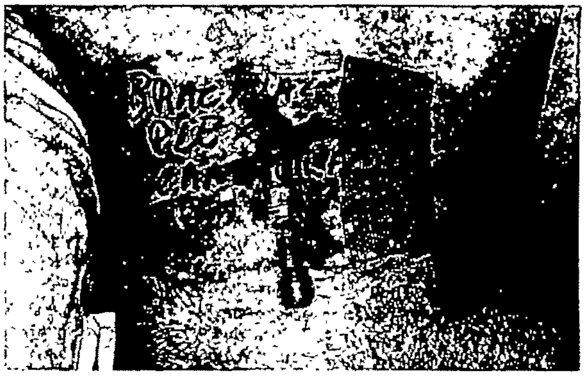

FIG. 1. Clear labelling of cannula placed in left brachial plexus sheath.

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vacaine via the *in situ* cannula. A thrombus was removed from the vein graft. The patient was transferred to the ward with the brachial plexus cannula *in situ*. During the night, the house officer on duty was called to administer i.v. antibiotics. He dissolved flucloxacillin 500 mg in sterile water 10 ml and injected this into the brachial plexus cannula. The patient complained of tingling and pain in his shoulder during the injection. The following morning the staff nurse on duty realized the house officer's mistake and informed the surgical and anaesthetic teams. Twenty millilitre of normal saline with 0.25% bupivacaine 20 ml were injected into the brachial plexus sheath to dilute any remaining antibiotic, as recommended by Tuohy and MacEvilly [1]. When the local anaesthesia had worn off, neurological examination of the arm was carried out. This was normal. During the next few days, the condition of the thumb deteriorated because of graft thrombosis, and it was amputated. Follow-up by the Anaesthetic Department was continued for 1 month. No adverse sequelae were noted.

DISCUSSION

Flucloxacillin sodium is formulated in a white powder for dissolving in 2 ml of sterile water. The antibiotic and the high sodium content of the solution may be irritant to neural tissue. In a literature search, we found no reference to accidental injection of this antibiotic solution into the brachial plexus. There are, however, several reports of inappropriate injections into the brachial plexus sheath, arteries and the extradural space [1, 2].

Active management to prevent potentially harmful effects includes [1]:

(1) Dilution of the injected substance by isotonic saline.

(2) Injection of bupivacaine to provide analgesia and vasodilatation, which enhances absorption of the antibiotic.

(3) Injection of hyaluronidase has been described to aid dispersal and hasten absorption of antibiotic [1]. This was not undertaken in our patient because we wished to minimize the amount of foreign material injected around the neurovascular bundle.

(4) Stellate ganglion block has been recommended when vascular damage is suspected, in order to improve blood flow to the limb [1, 3]. We did not consider this necessary in our patient, as a brachial plexus block was already present for postoperative analgesia and to maximize blood flow to the limb.

(5) Dexamethasone is thought to minimize tissue destruction after inadvertent injection of thiopentone [1]. We were concerned mainly with direct injury to the neural plexus, rather than widespread tissue damage, and therefore did not believe that steroids would be useful.

(6) Symptomatic measures such as bed rest and elevation of the limb and analgesics.

This incident may have been prevented if we had used an extradural catheter rather than an i.v. cannula. We believe that blood should be aspirated from i.v. cannulae or catheters placed in either the internal jugular or subclavian vein before injection of foreign substances.

We hope that the report of this case may promote greater vigilance in labelling and use of catheters and cannulae used for local anaesthetic purposes.

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INTRAVENTRICULAR DIAMORPHINE VIA AN OMMAYA SHUNT FOR INTRACTABLE CANCER PAIN

W. G. REEVE AND J. G. TODD

SUMMARY

We describe two patients in whom diamorphine was administered into the intraventricular space via an Ommaya reservoir, producing excellent pain relief. The use of this technique for long term administration of analgesia is reviewed.

KEY WORDS

Analgesics: intraventricular diamorphine. Pain: intractable, cancer

The Ommaya reservoir, described first in 1963 [1], was developed to allow the repeated introduction into the CSF of drugs such as antibiotics or cancer chemotherapy agents [2]. In 1982 Leavens and colleagues reported the administration of intraventricular morphine via an Ommaya shunt [3], but intraventricular administration of diamorphine has not been described previously. We report its use in two patients. Despite excellent pain relief, the technique failed to prevent a withdrawal syndrome when systemic opioids were stopped.

CASE REPORTS

Patient 1

A 52-yr-old man presented in October 1986 with a 2-yr history of progressive weakness and painful paraesthesiae in both legs. He had a past history of removal of right cerebellar haemangioblastoma in 1955, from which he had made a good recovery. Spinal magnetic resonance imaging (MRI) showed an extensive intramedullary lesion extending from C5 to T9. The patient underwent a midline dorsal myelotomy and removal of an intermediate grade astrocytoma. In July 1987, a new left cerebellar haemangioblastoma was diagnosed and subsequently excised. Later a repeat MRI scan showed a cystic recurrence of the astrocytoma, but further surgery was not considered.

By October, the patient's main problem was bilateral leg pain, neuropathic in nature and more severe on the right. This was associated with objective sensory loss from T1 to L5 on the right side, increased tone and leg weakness. However, he was able to walk with a stick and was continent. By January 1988 his symptoms had progressed to bilateral leg, neck, upper back and shoulder pain which prevented sleep. The pain was relieved only partially by morphine sulphate (MST Continus tablets) 60 mg 8-hourly, codeine phosphate 60 mg 4-hourly, dexamethasone 4 mg 12-hourly, diazepam 5 mg 8-hourly and mianserin 60 mg at night. Neither transcutaneous nerve stimulation nor guanethidine block produced lasting benefit.

A lumbar intrathecal test dose of diamorphine 2 mg brought good relief of his leg pain but, as expected, no relief of interscapular pain. An Ommaya reservoir (Heyer–Schulte, silicone, burr hole design) was inserted via a right frontal burr hole. A subsequent CT scan showed the tip of the catheter in the third ventricle. Instillation of diamorphine 5 mg produced good pain relief. Over the next few days oral opioids were stopped. Two days later he developed a withdrawal reaction with severe abdominal cramps, diarrhoea, sweating, tachycardia, hypertension, anxiety and restlessness. This was relieved by parenteral administration of opioids, followed by MST Continus 30 mg 12-hourly. Intraventricular diamorphine resulted in improved analgesia and a

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smaller dose of oral opioids, with his previously distressing constipation controlled. The duration of pain relief was up to 4 weeks. Repeated injections into the reservoir were made on a monthly outpatient basis. As a result of progression of the disease and analgesic tolerance, his opioid requirements increased steadily until November, when he received a monthly bolus of diamorphine 17 mg in water 0.5 ml into the reservoir, together with MST Continus 90 mg 8-hourly. Six months later the increasing requirement for oral opioids caused doubt as to the benefit of intraventricular opioids, so administration was stopped. This was followed by return of intolerable pain, relieved only by intraventricular diamorphine.

The patient suffered no complications from the reservoir and only minor, short-lived side effects after top-ups. These were vomiting and drowsiness commencing 30 min after injection and lasting for 4 h. There was no respiratory depression and the reservoir was still *in situ* 21 months after insertion.

Patient 2

A 13-yr-old girl was diagnosed as having nodular sclerosing Hodgkins lymphoma, stage 2a, in June 1986. Despite repeated courses of chemotherapy and radiotherapy, her disease remained active. By April 1988 a mass in her left axilla, extending to the side of the neck, had invaded the brachial plexus. She was suffering from severe pain in the fingers of her left hand, arm and scapular region. By June 1988 she had developed bilateral ankle clonus caused by spread of disease to the cervical vertebrae and spinal cord. Despite MST Continus 180 mg 12-hourly, combined with dextromoramide 5 mg during periods of activity, her pain was relieved only partially and she was commenced on a continuous subcutaneous infusion of diamorphine 12 mg h^{-1}. An Ommaya reservoir was inserted via a right frontal burr hole under general anaesthesia. After the instillation of diamorphine 3 mg she was pain free. After weaning from the diamorphine infusion she was discharged from hospital. The next day she developed diarrhoea, vomiting and insomnia. She was readmitted 4 days later "feeling suicidal", but still pain free. A diagnosis of opioid withdrawal syndrome was made and her sleep pattern improved only after recommencement of systemic opioids. She was discharged with oral morphine sulphate 30 mg twice daily plus haloperidol.

Her pain control was excellent for 4 weeks after the initial intraventricular injection; her quality of life improved and she was able to resume horse riding. After 4 weeks she received further top-ups of diamorphine 2–3 mg every 10 days. Each administration produced complete pain relief, but the duration of action decreased. During the terminal phase of the illness, her condition became too poor to warrant frequent hospital attendance, so intraventricular administration ceased. Subcutaneous diamorphine was recommenced and she eventually died in December 1988.

DISCUSSION

These two patients highlight several aspects of long term intraventricular administration of opioids.

There is an acceptably low morbidity and mortality associated with insertion of the reservoir [2]. Strict aseptic precautions are taken each time the reservoir dome is punctured, because of the risk of meningitis. The risks are outweighed by the potential dangers and neurological deficits linked to major ablative procedures used in the management of diffuse pain caused by orofacial, neck and disseminated cancer [4].

The incidence of opioid side effects is acceptably low. Previously reported side effects include urinary retention, somnolence, visual hallucinations, pruritis and facial tingling lasting usually for a few hours [5, 6]. Patient 1 demonstrated the absence of gastrointestinal side effects.

Respiratory depression is uncommon after intraventricular morphine. Only two cases have been reported [4, 5], both antagonized easily by naloxone. To assess the likelihood of respiratory depression, together with the quality and duration of pain relief, a test dose of lumbar intrathecal opioid is advised. A suitable test dose comprises 1% of the patient's usual morphine requirement [6]. Because of the theoretical risk of respiratory depression, we avoided pumping the reservoir, to prevent a bolus dose being delivered into the ventricle. These patients had ECG and ventilatory frequency monitored in the ward for 2 h after intraventricular administration of drug (which was administered by one of the authors (J. G. T.)), and were allowed home 6 h later. However, other workers have trained the family of their patients to perform the technique at home [3, 6].

Diamorphine may have advantages over morphine. The white crystalline powder diamorphine hydrochloride is highly soluble in water and is preservative free. The selected dose may be dissolved in 0.2–0.5 ml of water or saline immediately before injection into the reservoir.

In our two patients the long duration of pain relief exceeded the usual duration of up to 48 h reported for intraventricular morphine; this is difficult to explain. It takes some time for the drug to diffuse out of the reservoir, but the rate of diffusion is unknown. The action of diamorphine is continued by its active metabolites, monoacetyl morphine and morphine [7]. Intraventricularly administered morphine probably acts at a supraspinal level, and the short latency of analgesia is consistent with this hypothesis. Analgesia may be continued by caudal diffusion resulting in a direct spinal action [4]. The interactions of endogenous and exogenous opioids with their different receptor populations are complex, but activation of endogenous opioid systems may be involved in analgesia of longer duration than predicted by pharmacokinetics [8]. "Permanent" analgesia produced by intraventricular morphine has been reported previously [4].

The duration of pain relief in both patients decreased with subsequent administration because of a combination of progression of disease and development of tolerance. It is possible that more effective long term analgesia may have been achieved by increasing the frequency of intraventricular top-ups, rather than by increasing systemic administration.

Most patients embarking on this therapy are already receiving opioid analgesics and there is cross tolerance between systemic and intraventricular opioids. For this reason, reduction or discontinuation of systemic opiates has been advised before initiation of intraventricular therapy [4]. Experience in our patients suggests that it is undesirable to stop systemic opioids, as intraventricular diamorphine, although providing excellent analgesia, does not necessarily prevent abstinence syndrome. In monkeys, opioid withdrawal symptoms are believed to be mediated by increased noradrenergic activity at the midbrain coeruleus [9]. The reduction of withdrawal symptoms by clonidine [10] suggests that the same mechanism occurs in man.

Glucose utilization in the limbic system increases during experimental withdrawal of opioids, with a distribution similar to naloxone binding site distribution [11]. This is consistent with the finding that neither spontaneous withdrawal in these patients, nor naloxone [4, 5], antagonized the analgesia of intraventricular opioids. The development of withdrawal in these patients suggests that the concentration of active opioid at CNS receptors involved in physical dependence was insufficient to prevent withdrawal. Experimentally induced lesions of the fasciculus retroflexus in the interpeduncular nucleus increase the diarrhoea of opioid withdrawal, suggesting a central component of this symptom—probably an interaction between the limbic system and the dorsal motor nucleus of the vagus [12]. However, the characteristics of opioid dependence in isolated guineapig ileum closely resemble those of dependence in whole animals [13]. This supports the suggestion that lack of opioid at gut mu receptors contributed to the increased gut motility and gastrointestinal symptoms.

It is clear that the balance between analgesic and unwanted effects depends upon many factors. The opioid concentration at different central and peripheral receptor sites appears to be important and may be influenced by route of administration.

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ACUTE PULMONARY OEDEMA FOLLOWING ADMINISTRATION OF ORNITHINE-8-VASOPRESSIN

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SUMMARY

We report the case of a patient who developed acute pulmonary oedema following a short and uneventful surgical procedure. Among the differential diagnoses, the role of ornithine-8-vasopressin is emphasized.

KEY WORDS
Complications: pulmonary oedema. Hormones ornithine-8-vasopressin.

Ornithine-8-vasopressin ([Orn^8]-VP) (POR-8, Sandoz) a synthetic derivative of vasopressin, is used frequently as a local vasoconstrictor in preference to adrenaline [1, 2]. Compared with natural vasopressin, [Orn^8]-VP is characterized by enhanced pressor actions and reduced antidiuretic effects [3]. Common side effects include pallor of the skin, nausea and vomiting, increased gut motility, hypertension and reflex bradycardia [4]. Large doses administered i.v. induce coronary vasoconstriction and ischaemia of the gravid uterus [5]. We report the unusual case of a patient who developed pulmonary oedema following local infiltration of [Orn^8]-VP 12 iu.

CASE REPORT

A 55-yr-old healthy, slightly obese woman (170 cm/75 kg) was scheduled to undergo elective haemorrhoidectomy. She had no known allergies and was not taking any medications. Her past medical history was unremarkable. A few years previously she had an uneventful appendicectomy and had surgery for a benign left breast cyst. Preoperative physical examination, ECG and chest x-ray were normal. Arterial pressure was 150/80 mm Hg. Laboratory blood tests were all in the normal range.

The patient was premedicated with pethidine 60 mg i.m. and atropine 0.5 mg i.m. Anaesthesia was induced with propofol 120 mg i.v. Suxamethonium 100 mg i.v. was used to facilitate tracheal intubation. Anaesthesia was maintained with alfentanil 250 µg i.v., and 0.9–1.1 % isoflurane and 66 % nitrous oxide in oxygen. She was also given vecuronium 4 mg i.v. and ventilation was controlled at a tidal volume of 700 ml and rate of 12 b.p.m. Monitoring included ECG, automated arterial pressure (Dinamap), pulse oximetry and end-tidal carbon dioxide. At the beginning of the procedure, the surgeon infiltrated the area with [Orn^8]-VP 12 iu diluted in isotonic saline 40 ml. Anaesthesia and surgery proceeded smoothly and lasted 30 min. During the operation end-tidal carbon dioxide was kept at 4.5–5.3 kPa and oxygen saturation did not decrease to less than 95 %. Slight pallor of the hands was noticed. Arterial pressure was 160–140/100–80 mm Hg and heart rate 70 beat min^{-1}. At the end of the procedure, neuromuscular block was antagonized with atropine 1.5 mg i.v. and neostigmine 2.25 mg i.v.

The patient started to breathe spontaneously, opened her eyes and was able to sustain head lift. The trachea was extubated and after 1 or 2 min she showed difficulty in breathing. On physical examination she was tachypnoeic (35 b.p.m.), sweating, with audible bilateral rales. Arterial pressure was 110/80 mm Hg. Central venous pressure was 5 cm H_2O. Her extremeties were pale. Chest x-ray and a thoracic body scan confirmed the diagnosis of pulmonary oedema (figs 1, 2).

The patient was transferred to the surgical intensive care unit (SICU) and the trachea was

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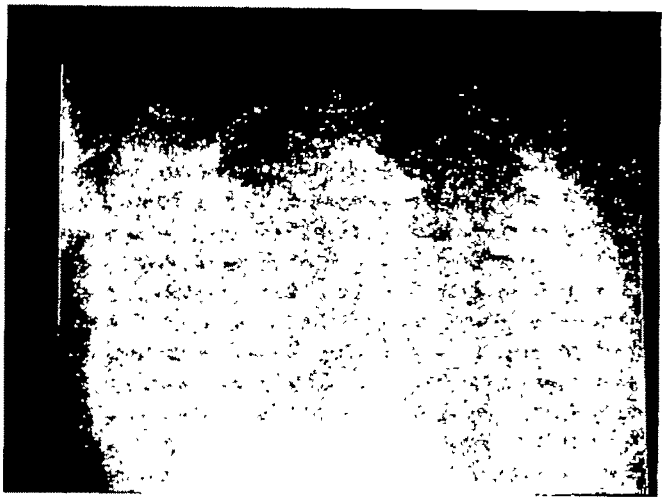

FIG. 1. Postoperative chest x-ray.

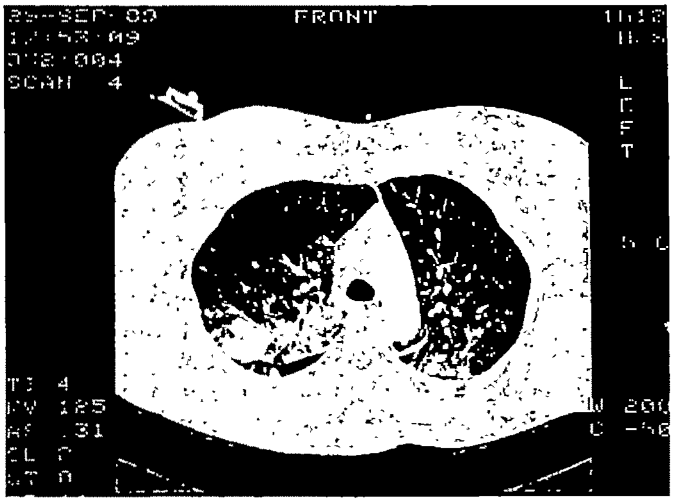

FIG. 2. Postoperative thoracic body scan.

reintubated after administration of midazolam 10 mg i.v. and vecuronium 12 mg i.v. She was sedated with midazolam 4–6 mg h^{-1} and the lungs ventilated with a tidal volume of 750 ml at a rate of 10 b.p.m. PEEP was applied (10 cm H_2O). Blood-gas analysis ($F_{I_{O_2}}$ 0.5) was: pH 7.36, P_{CO_2} 5.95 kPa and P_{O_2} 10.2 kPa. Moderate water restriction (Ringer lactate 1500 ml 24 h^{-1}) was ordered. The patient improved dramatically. Chest x-ray on the following day was normal (fig. 3).

The trachea was extubated 18 h after admission to the SICU and the patient was transferred to the general ward the same day. The remainder of her hospital stay was uneventful.

Serial ECG showed no signs of ischaemia, right or left ventricular overload and no rhythm or conduction disturbances. Blood tests were all in the normal range; in particular there was no increase in concentrations of cardiac enzymes (CK, CK-MB), no eosinophilia and no increase in IgE concentration. The search for specific IgE

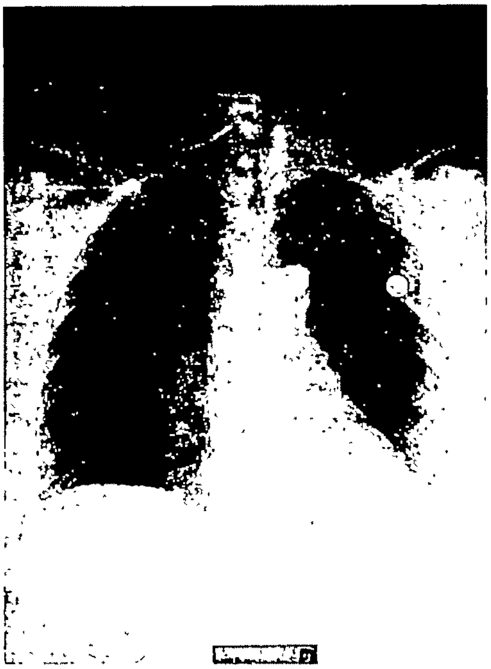

FIG. 3. Chest x-ray 18 h after that in figure 1.

anticholine antibodies was negative. Skin prick tests 6 weeks later with suxamethonium (0.1 ml of a 1-μg ml^{-1} solution), vecuronium, propofol, alfentanil, atropine and neostigmine were also negative. The C_1 esterase inhibitor (24 mg %) was within the normal range (11–26 mg %). All the components of complement (C_1/C_4) were also within the physiological range.

DISCUSSION

Acute pulmonary oedema in a previously healthy patient following an uneventful short anaesthesia and surgical procedure was unexpected. The absence of fever, chills, hypotension, the unremarkable WBC count and rapid resolution of the problem make sepsis unlikely. Failure of the left ventricle may be excluded in the face of normal haemodynamic variables and absence of heart murmur, gallop rhythm, ECG changes or increased concentrations of cardiac enzymes. The occurrence of a silent aspiration would have been diagnosed by changes in oxygen saturation, increased airway pressure and modification of the end-tidal carbon dioxide concentration curve. Obviously there was no major bleeding and the patient received only 1500 ml of Ringer lactate during the operation, excluding overload. The absence of fever, leucocytosis and signs of pulmonary infection makes the diagnosis of post-extubation aspiration of stomach contents unlikely. The differential diagnoses, therefore, include hereditary angioneurotic oedema (C_1 esterase inhibitor deficiency), anaphylactoid reaction to suxamethonium and a side effect secondary to injection of ornithine-8-vasopressin.

The C_1 esterase inhibitor was present in normal concentration (24 mg %) and had normal activity. The absence of a familial history is also an argument against hereditary angioneurotic oedema. Anaphylactic or anaphylactoid reactions to suxamethonium are unlikely in the presence of normal intradermal skin tests, the absence of eosinophilia and specific IgE anticholine antibodies; moreover, the lack of any personal or familial allergic history associated with the paucity of systemic effects and the rapid clinical resolution also argue against such a diagnosis [6]. All drugs used during the surgical procedure gave negative skin tests, making allergic reaction unlikely.

Pulmonary oedema is a common clinical emergency. According to Starling's equation, causes include increased pulmonary capillary pressure, decreased oncotic pressure, altered permeability or lymphatic insufficiency [7]. Non-cardiogenic pulmonary oedema is usually secondary to increased pulmonary vascular permeability and may also be caused by volume overload or, less commonly, by increased pulmonary capillary pressure secondary to pulmonary venous disease. The latter is compatible with the physiological actions of [Orn^8]-VP. Indeed, this synthetic polypeptide has a specific potent vasoconstrictor action on capillaries and veins [3]. Pharmacological features of [Orn^8]-VP include maximal effect in about 10–15 min and duration of action more than 90 min [8], and these are also compatible with a direct causal effect of [Orn^8]-VP in inducing acute pulmonary oedema in this patient.

The manufacturers suggest administration of [Orn^8]-VP in a concentration of 1 iu per 10 ml. They also state that 5 iu (maximum recommended dose) in 50–60 ml gives excellent results. However, no absolute or body weight limits are recommended. In burned children, Lamont and Yorke [9] suggested 0.5 iu kg^{-1} as the maximum dose, with an upper limit of 15 iu/30 kg. No such data are available for adults. Nevertheless, the local infiltration of 12 iu (0.15 iu kg^{-1}) for a perineal block in a healthy adult may be associated with serious pulmonary complications. In our patient, inadvertent i.v. injection may have been a factor contributing to severe venopulmonary vasoconstriction. Despite the lack of data in the literature on the maximum safe dose of ornithine-8-vasopressin for adults, it would seem reasonable to administer no more than 0.1 iu kg^{-1} by local infiltration.

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COMPARISON OF PULSE OXIMETERS: ACCURACY AT LOW ARTERIAL PRESSURE IN VOLUNTEERS

R. J. FALCONER AND B. J. ROBINSON

SUMMARY

A laboratory model was developed of limb hypoperfusion in volunteers, using partial occlusion of the brachial artery with consequent reduction in radial artery pulse pressure. This was used to compare the function of 13 pulse oximeters and the effect of reduced pulse pressure and mild hypoxia on these devices. With the exception of one device, all the pulse oximeters studied demonstrated similar accuracies at pulse pressures exceeding 20 mm Hg. There were however, significant differences between several of the pulse oximeters in both ability to display readings and accuracy of readings displayed when brachial artery occlusion reduced radial artery pulse pressures equal to or less than 20 mm Hg.

KEY WORDS

Equipment: pulse oximeters. Monitoring: pulse oximeters, arterial pressure.

The reliability of pulse oximetry measurements may be affected by factors which include the nature of the haemoglobin present (e.g. methaemoglobin, carboxyhaemoglobin), movement artefacts and low peripheral perfusion. Several studies have assessed the accuracy of pulse oximeters in volunteer subjects during induced desaturation [1, 2] and in neonates [3] and adults [4]. Other studies have assessed the accuracy of pulse oximeters and the effects of peripheral hypoperfusion both in volunteers [5–7] and in patients immediately after open heart surgery [8, 9]. However, the methods used may be inappropriate; volunteer studies which use arterial tourniquets to reduce the pulse pressure [5, 6] are of doubtful validity. Venous congestion caused by the tourniquet can cause pulsatile venous flow which may be detected by the pulse oximeters as arterial pulsation and result in falsely low readings of "arterial" saturation [10]. One other study has compared pulse oximeters using cold-induced peripheral vasoconstriction (cold-pressor response) [7]. This model may not be representative of the cardiovascular events that occur during operative procedures as there is no concomitant reduction in cardiac output and there is an increase in arterial pressure. In studies of patients after cardiac bypass [8, 9], there may also be problems with temperature dependent changes in performance of the LED and photodetector components of the pulse oximeter probe [11]. Also, any reduction of arterial pressure in these patients is uncontrolled and there may be pathophysiological changes in the peripheral circulation of some.

In this study we describe a laboratory model of limb hypoperfusion by partial occlusion of the brachial artery which avoids venous congestion. We used this model, combined with mild hypoxia induced by breathing hypoxic gas mixtures, to compare in healthy volunteers the accuracy of several currently available pulse oximeters.

SUBJECTS AND METHODS

The study was approved by the Wellington Hospital Board Ethics Committee. Informed consent was obtained from nine volunteers aged 25–45 yr (two female, seven male; eight Caucasian, one Chinese). Three of the volunteers participated on two occasions 5, 13 and 14 weeks apart. One of the volunteers participated on three

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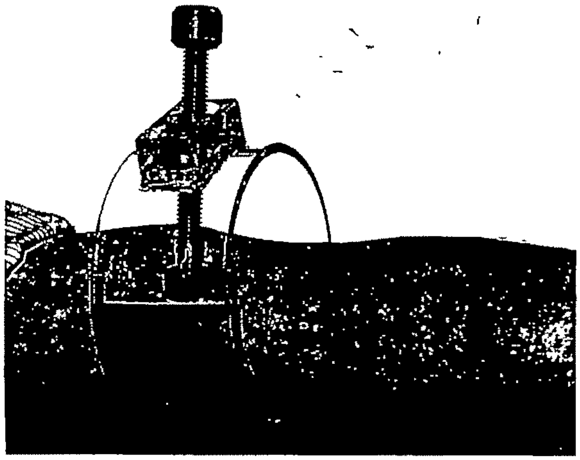

FIG. 1. Device for occluding the brachial artery.

occasions separated by intervals of 7 and 10 weeks, respectively. All other volunteers participated on one occasion. Volunteers were excluded if they had a history of cardiovascular disease, smoked within the previous 48 h, or had an aberrant arterial configuration at the wrist as demonstrated by Allen's test.

A 22-gauge cannula was inserted into the radial artery of the non-dominant hand under local anaesthesia for blood sampling and for direct measurement of arterial pressure (Hewlett-Packard; model 1029A transducer, model 78342A monitor). Arterial pulse pressure was reduced during the study by using a specially made clamp which encircled the arm at the elbow and pressed a disc (22 mm diameter) onto the skin over the brachial artery (fig. 1). This clamp was threaded so that the degree of arterial compression and occlusion could be adjusted, leading to a controlled reduction in arterial pressure, which was measured at the wrist. The pulse pressure (systolic pressure minus diastolic pressure) was used to quantify the degree of hand perfusion. The subjects were supine and the cannulated arm rested on a padded surface at heart level.

Pulse oximeter probes were attached randomly to different fingers of the subject. Probes were covered to prevent interference from adjacent probes and room lighting. Blood samples from the arterial cannula were drawn into heparinized syringes and Sa_{O_2} measured immediately using a co-oximeter (OSM 2 Hemoximeter, Radiometer Copenhagen). Immediately before each blood sample was taken, the Sa_{O_2} readings displayed by each pulse oximeter were recorded, with systolic and diastolic arterial pressures displayed on the arterial pressure monitor. Recordings were repeated both under resting conditions and with occlusion of the brachial artery. Hypoxia was induced in the volunteer by breathing a hypoxic gas mixture (12–14% oxygen in nitrogen) from pre-filled 300-litre Douglas bags via a non-rebreathing valve. When hypoxia reached a steady state from the results of three serial arterial haemoglobin oxygen saturation determinations (all within 2%), further blood samples were taken at approximately 1-min intervals with simultaneous recordings of pulse oximeter readings and arterial pressure. Recordings were repeated with limb pulse pressure reduced. The subject remained hypoxic (Sa_{O_2} between 88% and 80%) for several minutes and achieved resaturation between sets of recordings by breathing 100% oxygen. At approximately 20-min intervals, the pulse oximeter probes were removed for 5 min to avoid gradual compression of the fingers by the probes. After 5 min the probes were reattached so as to be tested in turn on each finger. The finger to which each probe was attached was noted.

Thirteen pulse oximeters were used in the study: Biochem 1040a, Criticare 504US, Critikon Oxyshuttle, Datex Satlite, Kontron 7840.2, Nellcor N100, Nellcor N200, Novametrix 505, Ohmeda 3700, Physiocontrol 1600, Radiometer Oxi, Sein Se200, Simed S100. Not all pulse oximeters were tested on all subjects. Wherever possible, pulse oximeters were set up with the fastest Sa_{O_2} display averaging times (e.g. 3 s) active. When the Nellcor N200 was used with the ECG cable attached to the volunteer (Nellcor N200+ecg), a semi-disposable probe (N-25) was used as requested by the manufacturer; otherwise a standard finger probe was used when this unit was used without the ECG (Nellcor N200−ecg). The Criticare 504US was evaluated also with (Criticare 504US+ecg) and without (Criticare 504US−ecg) the ECG cable attached to the volunteer. The Radiometer Oxi was used only with a multi-site flex probe. With all other pulse oximeters the standard multi-use finger probe was used. One pulse oximeter unit was evaluated for each model tested with the exception of the Nellcor N200−ecg and Simed S100 for which two units of both were evaluated. Although the software was different for the units of both models, there was no significant difference between the results of each model and therefore data were combined.

TABLE I. *Numbers of observed and expected correct, incorrect and missing readings for the Sein SE200 pulse oximeter. χ^2 was calculated from the observed and expected correct, incorrect and missing readings except at *pulse pressures greater than 10 mm Hg, for which incorrect and missing readings were combined since the values in some of these cells were less than 5*

Pulse pressure (mm Hg)	Total observations	Correct			Incorrect			Missing		
		Observed	Expected	χ^2	Observed	Expected	χ^2	Observed	Expected	χ^2
≤10	133	25	74.4	32.8	70	40.7	21.09	38	18.2	21.54
>10 to ≤20	45	7	26.8	14.63	32	16.2	20.34*	6	2.0	*
>20	88	24	60.8	22.7	63	27.0	50.16*	1	0.02	*

TABLE II. *Pulse oximeter performance at pulse pressures equal to or less than 10 mm Hg. $\chi^2 = (\text{Observed} - \text{expected})^2/\text{expected}$. Values of $\chi^2 > 3.83$ may be considered significant ($P < 0.05$)*

Pulse oximeter	Total observations	Correct			Incorrect			Missing		
		Observed	Expected	χ^2	Observed	Expected	χ^2	Observed	Expected	χ^2
Biochem 1040a	115	67	59.3	1.00	40	39.6	0.23	8	16.1	4.08
Datex Satlite	180	127	97.0	9.28	47	50.8	0.28	6	32.1	21.22
Criticare 504US+ecg	62	42	33.6	2.10	20	20.0	0.00	0	8.4	8.40
Criticare 504US−ecg	49	34	36.0	0.06	15	10.3	2.14	0	2.1	2.10
Critikon Oxyshuttle	195	124	127.6	0.10	52	48.3	0.28	19	18.8	0.00
Kontron 7840.2	162	131	111.3	3.49	31	32.3	0.05	0	18.4	18.40
Nellcor N100	193	55	92.5	15.20	60	54.3	0.60	78	45.0	24.20
Nellcor N200+ecg	99	74	64.0	1.56	24	24.9	0.03	1	9.1	7.21
Nellcor N200−ecg	35	5	11.8	3.92	3	12.5	30.01	27	10.9	23.78
Novametrix 505	215	124	121.2	0.06	29	32.7	0.42	62	58.2	0.25
Ohmeda 3700	144	82	71.4	1.57	48	39.5	1.83	14	33.0	10.94
Physiocontrol 1600	141	48	62.4	3.32	17	43.3	15.97	76	36.3	43.42
Radiometer Oxi	36	12	9.6	0.60	24	13.0	9.31	0	14.4	14.40
Simed S100	183	100	115.1	1.98	52	47.6	0.04	31	20.0	6.05

Statistics

The results were categorized according to whether the pulse oximeter reading was correct (within 3% of the arterial blood sample), incorrect (outside 3% of the blood sample) or missing (no reading given). An Sa_{O_2} accuracy of "within 3%" was calculated from the variance of reported accuracy of the pulse oximeter and co-oximeter manufacturer's specifications; both device types have an accuracy of 2% at Sa_{O_2} values greater than 80%. The variance was calculated as:

$$\sqrt{2\%^2+2\%^2} = \sqrt{8\%} = 2.83\%.$$

Using the results of two pulse oximeters (Datex Satlite and Critikon Oxyshuttle) from all nine subjects, there were marked differences between subjects at low (equal to or less than 20 mm Hg) pulse pressures in the number of correct, incorrect and missing readings. Therefore the numbers of expected correct, incorrect and missing readings were calculated for each subject, under the hypothesis that there were no differences between devices, for pulse pressures greater than 20 mm Hg, 11–20 mm Hg or equal to or less than 10 mm Hg. This was calculated from the total number of observed correct, incorrect and missing readings for all devices for each subject. The number of expected and the number of observed correct, incorrect and missing readings were summed across all subjects for each device. The numbers of expected and observed readings were compared using chi-square, with $\chi^2 > 3.83$ considered significant (i.e. $P < 0.05$).

RESULTS

We collected 3509 individual data points. The Sein Se200 was found to operate in an extremely erratic manner, despite no occlusion of the brachial artery (table I). As it had not been used on all subjects, inclusion of its data distorted the expected observations of correct, missing and incorrect readings of some subjects and it was therefore eliminated.

Excluding the Sein Se200, there were no significant differences between the devices at pulse pressures greater than 20 mm Hg. At pulse pressures of 11–20 mm Hg the Physiocontrol 1600 gave fewer correct (observed 9, expected 17.5, $\chi^2 = 4.13$) and more incorrect or missing (observed 11, expected 6.9, $\chi^2 = 4.05$) readings than expected. There were no other differences between the devices at this pulse pressure.

At pulse pressures equal to or less than 10 mm Hg, significant differences were found between many of the devices (table II). The percentages of correct readings (within 3% of the co-oximeter measurement) more or fewer than expected at these pulse pressures are shown also in figure 2. The Datex Satlite was found to give more correct readings than expected ($\chi^2 = 9.28$); the Nellcor N100 and N200-ecg gave fewer correct readings than expected ($\chi^2 = 15.20$ and 3.92, respectively).

The percentages of incorrect readings (outside 3% of the co-oximeter measurement) are shown in figure 3. The Radiometer Oxi was found to give more incorrect readings than expected ($\chi^2 = 9.31$). The Nellcor N200–ecg and Physiocontrol 1600 gave fewer incorrect readings than expected ($\chi^2 = 30.01$ and 15.97, respectively).

The percentages of missing readings (no reading displayed on the oximeter) are shown in figure 4. The Radiometer Oxi ($\chi^2 = 14.40$), Datex Satlite ($\chi^2 = 21.22$), Criticare 504US+ecg ($\chi^2 = 8.40$), Ohmeda 3700 ($\chi^2 = 10.94$), Kontron 7840.2 ($\chi^2 =$

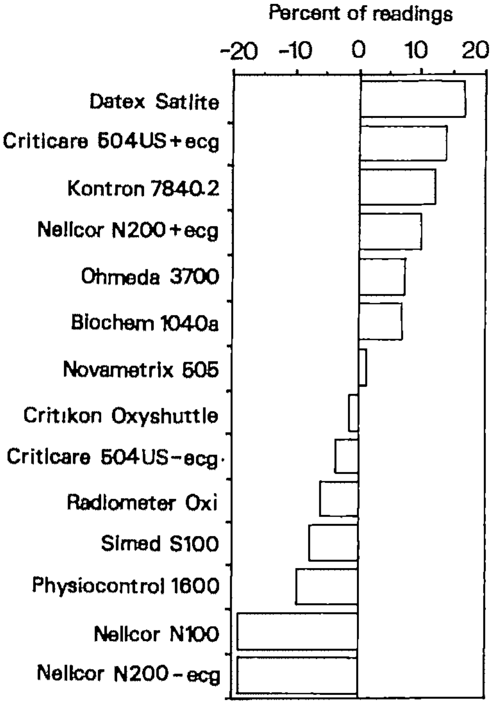

FIG. 2. Percentage of correct readings more (right of 0) or fewer (left of 0) than expected at pulse pressures equal to or less than 10 mm Hg for the pulse oximeters evaluated. The oximeters are ranked according to the percentage of correct readings more or fewer than expected.

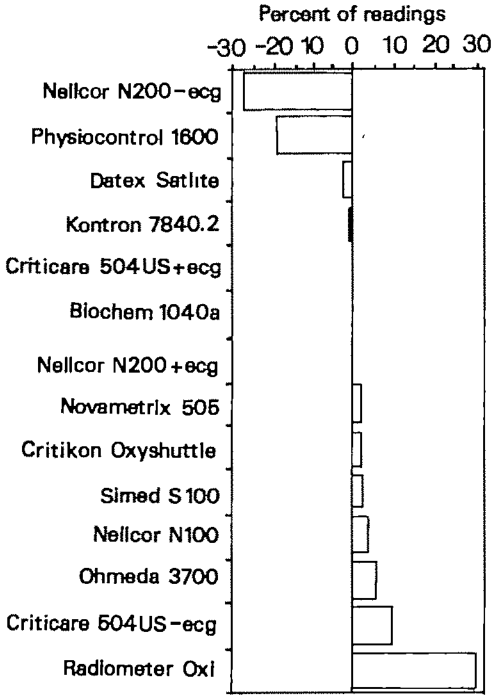

FIG. 3. Percentage of incorrect readings more (right of 0) or fewer (left of 0) than expected at pulse pressures equal to or less than 10 mm Hg for the pulse oximeters evaluated. The oximeters are ranked according to the percentage of incorrect readings more or fewer than expected.

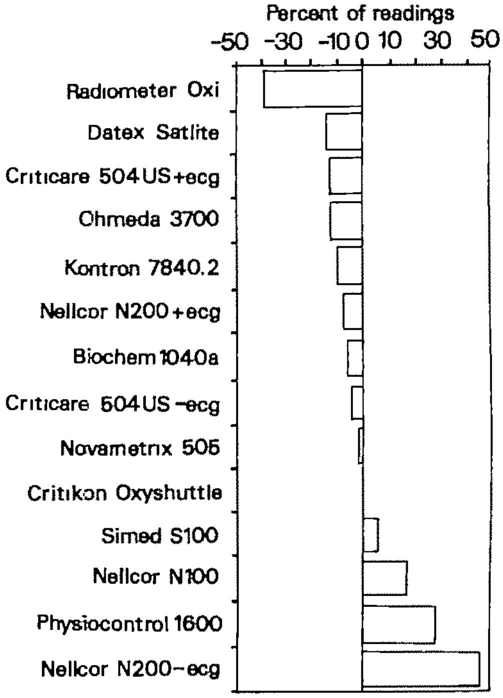

FIG. 4. Percentage of missing readings more (right of 0) or fewer (left of 0) than expected at pulse pressures equal to or less than 10 mm Hg for the pulse oximeters evaluated. The oximeters are ranked according to the percentage of missing readings more or fewer than expected.

18.40), Nellcor N200+ecg ($\chi^2 = 7.21$) and Biochem 1040a ($\chi^2 = 4.08$) were observed to miss fewer readings than expected. The Simed S100 ($\chi^2 = 6.05$), Nellcor N100 ($\chi^2 = 24.20$), Physiocontrol 1600 ($\chi^2 = 43.42$) and Nellcor N200−ecg ($\chi^2 = 23.78$) missed more readings than expected.

Studies were repeated on two or three occasions in four subjects. In all of these studies at least one pulse oximeter was used during two of the studies. Results obtained for a single pulse oximeter used on the same subject on the two occasions were comparable, suggesting the method is reproducible within subjects. We also ranked the function of each device according to the χ^2 values for correct, incorrect and missing readings from the group results and compared this with the ranking of the χ^2 values of the devices within individuals. The ranking of the devices from the grouped results was found to be comparable to the ranking of devices within individuals. The function of each pulse oximeter within subjects was not related to the finger used and was not affected by previous arterial cannulation.

DISCUSSION

We have created a simple model of peripheral hypoperfusion in volunteer subjects by partial occlusion of the brachial artery. This method reduces the arterial pressure which is measured directly at the radial artery and quantified by measuring the amplitude of the pulse wave (pulse pressure). Arterial blood samples were measured with a co-oximeter and mild hypoxia induced in volunteers in order to assess the accuracy of pulse oximeters during reduced blood flow to the probe site. The radial artery cannula did not affect the function of the pulse oximeters, as the accuracy of readings within individuals was not affected by the finger used. The number of repeated cannulations did not affect the function of the pulse oximeters, which suggests that no significant radial artery obstruction was present when the repeat studies occurred.

Brachial artery occlusion reduces the pulse pressure and thus there is a reduction in the size of the signal (i.e. pulse pressure wave) that the pulse oximeters use to calculate the Sa_{O_2}. This situation is similar to that observed in patients with reduced cardiac output, hypotension or peripheral vasoconstriction. Previous studies investigating the effect of reduced blood flow on pulse oximeters have used arterial or venous tourniquets [5–7] which result in venous congestion. In these situations the inaccuracy of the devices is likely to be caused by increased noise (e.g. venous pulsation) in addition to a reduced signal. Although venous congestion may occur clinically, it is encountered rarely and the main concern of anaesthetists is to obtain reliable readings from a pulse oximeter when a patient has reduced arterial pressure or peripheral vasoconstriction. The reduction of pulse pressure in our volunteers is therefore more likely to simulate the adverse conditions for pulse oximetry encountered in clinical practice.

The Sein Se200 was found to function in an erratic manner despite no arterial occlusion. This device was significantly different from all other devices and its lack of accuracy at normal arterial pressures is of some concern.

Under the null hypothesis from the results of the pulse oximeters other than the Sein SE200 we were able to produce the profile for an "average" pulse oximeter against which to compare all the devices. There were statistically significant differences between many of the devices at pulse pressures less than 20 mm Hg. Many of the pulse oximeters functioned quite accurately to low arterial pressures, whereas other devices gave either inaccurate or missed readings. At pulse pressures equal to or less than 10 mm Hg, the Datex Satlite was found to be more accurate than the average pulse oximeter and, conversely, the Nellcor N100 and N200 – ecg were found to be less accurate. Although the Physiocontrol 1600 and Nellcor N200 – ecg gave fewer incorrect readings than the average pulse oximeter at pulse pressures equal to or less than 10 mm Hg, these devices also missed more readings than expected. This could be considered a desirable feature; lack of a reading is perhaps better than an inaccurate reading when a patient becomes hypotensive or has vasoconstriction. We also observed that the ECG synchronization improved the performance of the Criticare 504US and Nellcor N200, although different probes were used in the latter device. The results of the Radiometer Oxi should be regarded with caution, as a standard finger probe was not available for evaluation with this device and the use of multi-site flex probe may have affected the accuracy of the device in this study.

From our results it is possible to rank devices according to each specific function. The ideal pulse oximeter should have as many correct readings with as few incorrect or missing readings as possible, and an overall ranking could be created by weighting the relative importance of each of these functions.

ACKNOWLEDGEMENT

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NON-INVASIVE MONITORING OF FINGER ARTERIAL PRESSURE IN PATIENTS WITH RAYNAUD'S PHENOMENON: EFFECTS OF EXPOSURE TO COLD

T. S. KURKI, H. I. PIIRAINEN AND P. T. KURKI

SUMMARY

We studied the effects of exposure to cold on finger arterial pressure (FAP) measured by a finger arterial pressure monitor in 15 patients with Raynaud's phenomenon and in 15 healthy volunteers. The cold exposure induced vasoconstriction of the peripheral vascular bed as judged by the plethysmograph of a pulse oximeter and had marked effects on FAP values compared with upper arm arterial pressure. Immediately after the cold exposure, FAP decreased significantly ($P \leqslant 0.01$) in both groups. However, during the subsequent 20 min, FAP values increased in relation to upper arm pressure. Finally, FAP values were greater than upper arm pressure in the control individuals, but not in patients with Raynaud's phenomenon. These results have implications for non-invasive monitoring of arterial pressure by the finger pressure device. Clinically, significant problems may arise in the monitoring of FAP in patients with a systemic connective tissue disease affecting peripheral circulation.

KEY WORDS

Complications: cold exposure, Raynaud's phenomenon. Monitoring: finger arterial pressure.

Several studies have demonstrated the accuracy of the Finapres monitor in the monitoring of finger arterial pressure [1–5]. Most of these studies were conducted in healthy volunteers or patients with normal peripheral circulation. This device functions correctly provided the peripheral pulsatile arterial volume and flow are sufficient [4, 6]. Peripheral blood flow may be insufficient in severe occlusive arterial disease. However, it may be reduced intermittently by certain factors such as increased sympathetic tone, hypovolaemia, arterial spasm, exposure to some drugs or cold [5, 6]. Patients with Raynaud's phenomenon are especially sensitive to these factors. Exposure to low temperature may induce vasospasm and circulatory arrest in the digits of these patients. Finger colour may be affected during the episode, the most common sequence being initial pallor followed by cyanosis. Recovery takes place either spontaneously or after rewarming and is accompanied often by a period of rubor caused by reactive hyperaemia [7–11].

The purpose of our study was to evaluate the effects of exposure to cold on finger arterial pressure measured by the Finapres in patients with Raynaud's phenomenon and in healthy volunteers.

PATIENTS AND METHODS

We studied 15 patients (13 female) with a systemic connective tissue disease and 15 healthy female volunteers. All patients had a history of Raynaud's phenomenon. Seven patients had systemic lupus erythematosus, four mixed connective tissue disease, three undifferentiated systemic connective tissue disease and one scleroderma. Mean age in the control group was 38.4 (range 25–54) yr and in the patient group 55 (range 38–71) yr. Mean duration of disease in the patient group before the study was 14 (range 2–30) yr. Three of the patients had mild hypertension. The patients'

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TABLE I. *Medication received by 15 patients with Raynaud's phenomenon. NSAID = non-steroidal anti-inflammatory drugs*

Medication	No. patients
Oral corticosteroids	6
Antimalarials	3
NSAID	8
Vasodilators	3
Diuretics	2
β-Blockers	2

antirheumatic and antihypertensive drugs are listed in table I. Three patients were anaemic (Hb ⩽ 120 g litre^{-1}). Thirteen patients had hypersedimentation, five circulating rheumatoid factor and six hypergammaglobulinaemia. All volunteers and patients gave written informed consent. The study was approved by the local Ethics Committee.

Non-invasive finger arterial pressure (FAP) was monitored continuously with a finger arterial pressure device (Finapres, Ohmeda). The cuff was placed around the index or middle finger of the right hand. FAP values were compared with those from the oscillometric non-invasive arterial pressure (AP) recordings from the contralateral arm. Average systolic, diastolic and mean FAP values were calculated for each 20-s period during one oscillometric measurement cycle. The oscillometric automatic arterial pressure device (Cardiocap, Datex) was used in the 3-min repeat mode during the baseline period and in the 5-min mode thereafter. The oscillometric method is described elsewhere [12].

The effects of exposure to cold on volume changes and oxygen saturation in arterial blood of the fingers were assessed by measuring the plethysmographic amplitudes from both hands with two pulse oximeters (Satlite, Datex). The amplitudes were recorded as amplitude factors: $[(I\max - I\min)/I\max] \times 100$. Peripheral temperature was monitored from the tip of the fourth finger on both the right and left hands using a temperature probe (YS 1400, Yellowspring Instrument Co. Inc.) connected to a Cardiocap monitor.

Patients and volunteers waited in a warm room (temperature 23–24 °C) for 20 min before the start of the 10–15 min baseline monitoring period. During the cold exposure, the Finapres and pulse oximeter probes were disconnected from the exposed site, and were reconnected immediately afterwards. Exposure to cold was carried out by immersing the right hand in cooled water (4–5 °C) for a 20-s period [9]. Monitoring on the contralateral side continued during immersion. The period after cold exposure lasted until recovery (that is, when the values returned to baseline) or 30 min after exposure, whichever was first.

Data were collected before and after cold exposure until recovery. Values were recorded every 30 s for plethysmographic amplitudes, oxygen saturation and temperature, and every 3–5 min for oscillometric arterial pressure and the corresponding values of FAP.

Statistical analysis was performed using a one-way repeated measures analysis of variance to test changes within groups. Differences between FAP and non-invasive AP and Δt values (baseline °C − actual °C) were calculated. The paired *t* test was used to compare changes between groups. A non-parametric Mann–Whitney test was applied to non-parametric data. Results are expressed as mean (SD) and $P < 0.05$ was considered significant.

RESULTS

All healthy volunteers had finger pulses detectable by the plethysmograph of the pulse oximeter during the baseline period. Three patients had no detectable pulse at the beginning of the baseline period. Mean finger temperature in these patients was 24 °C compared with 27 °C in the other patients and 29 °C in the control subjects. One of these patients suffered from scleroderma and two from an undifferentiated connective tissue disease. The hands of these patients were warmed in a water bath (40 °C) for 5 min before the exposure to cold. Recovery time after cold exposure in the control group was 13 (SD 5) min. In seven of 15 patients, temperature had still not returned to baseline after 25 min. The hands of these patients were then warmed in water. The recovery time in the other patients was 24 (10) min. There was a significant difference in Δt values between controls and patients 15, 20 and 25 min after cold exposure (*t* test) (fig. 1).

The plethysmographic amplitudes (amplitude factors in %) were significantly smaller in the patient group ($P \leqslant 0.05$, Mann–Whitney) than in the control group during the baseline monitoring phase. The plethysmographic amplitudes decreased significantly in the exposed side after cold exposure in both the control ($P \leqslant 0.05$) and the patient group ($P \leqslant 0.01$). The amplitudes decreased in the non-exposed side also, but the

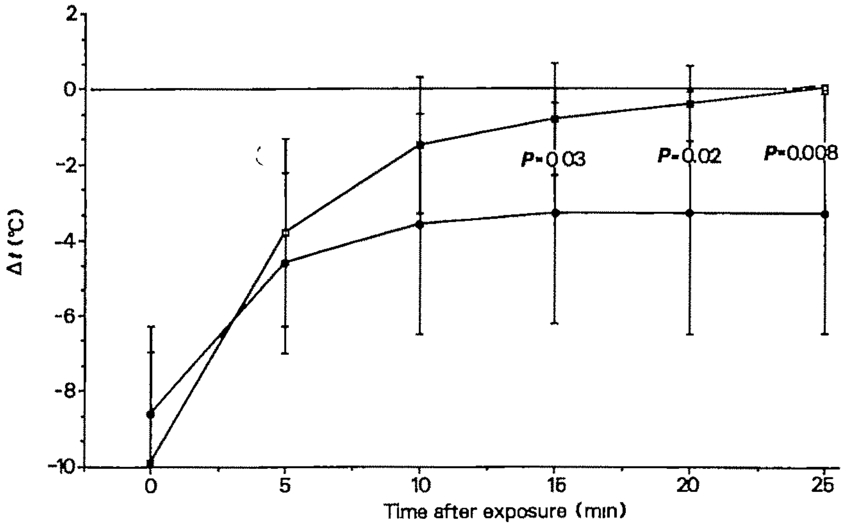

FIG. 1. Recovery of finger temperature from exposure to cold (mean (SD)). □ = Controls; ● = patients.

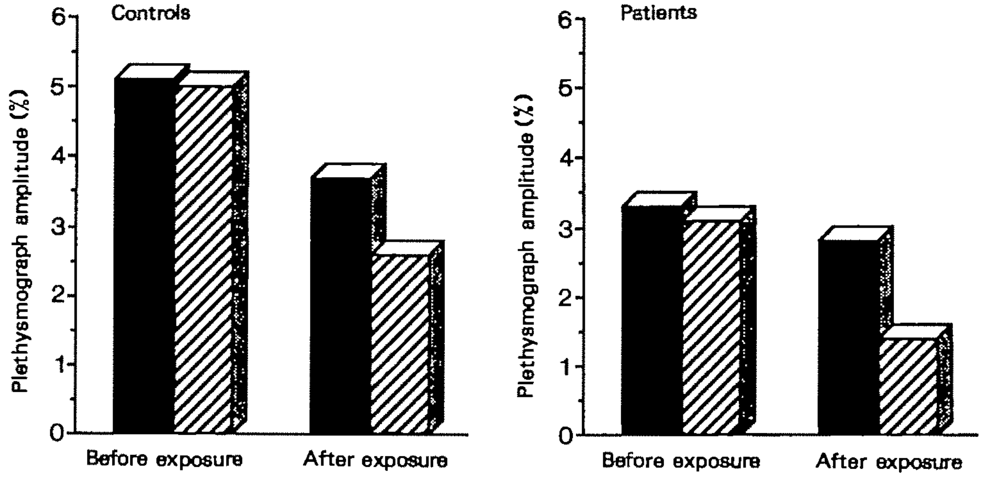

FIG. 2. Plethysmographic amplitudes (%) before and after exposure to cold in control subjects and in patients on the non-exposed (■) and the exposed (▨) side.

TABLE II. *Paired systolic (finger arterial–oscillometric) pressure differences (mean (SD) [range]) before and after exposure to cold*

	No. pairs	Pressure difference (mm Hg)			
		Patients	*P*	Controls	*P*
Baseline	150	−11(39)[−81 to 34]	0.28	4(11)[−11 to 18]	0.16
After exposure					
0	30	−18(29)[−65 to 21]	0.04	−18(18)[−45 to 20]	0.003
5 min	30	−9(47)[−110 to 48]	0.49	1(27)[−56 to 39]	0.84
10 min	30	−6(48)[−108 to 48]	0.68	7(27)[−57 to 57]	0.35
15 min	30	−2(36)[−73 to 44]	0.81	15(18)[−8 to 57]	0.02
20 min	30	−2(37)[−87 to 50]	0.83	19(20)[2 to 55]	0.03

TABLE III. *Paired diastolic (finger arterial–oscillometric) pressure differences (mean (SD) [range]) before and after the exposure to cold*

	No. pairs	Pressure difference (mm Hg)			
		Patients	*P*	Controls	*P*
Baseline	150	−5(18)[−35 to 25]	0.28	2(9)[−19 to 13]	0.4
After exposure					
0	30	−10(19)[−50 to 22]	0.08	−13(23)[−82 to 14]	0.04
5 min	30	−2(24)[−49 to 50]	0.76	3(16)[−34 to 23]	0.64
10 min	30	−6(18)[−48 to 19]	0.21	2(15)[−37 to 30]	0.64
15 min	30	−6(22)[−46 to 29]	0.37	5(12)[−11 to 29]	0.14
20 min	30	−9(21)[−50 to 25]	0.23	11(7)[−3 to 20]	0.004

TABLE IV. *Paired mean (finger arterial–oscillometric) pressure differences (mean (SD) [range]) before and after the exposure to cold*

	No. pairs	Pressure difference (mm Hg)			
		Patients	*P*	Controls	*P*
Baseline	150	−7(21)[−54 to 16]	0.22	4(10)[−11 to 27]	0.1
After exposure					
0	30	−9(18)[−40 to 16]	0.08	−15(25)[−79 to 9]	0.04
5 min	30	−10(33)[−77 to 41]	0.29	3(19)[−46 to 28]	0.62
10 min	30	−2(29)[−68 to 26]	0.79	8(21)[−39 to 54]	0.16
15 min	30	−4(23)[−43 to 17]	0.57	7(12)[−12 to 30]	0.08
20 min	30	−9(29)[−68 to 18]	0.24	10(17)[−15 to 24]	0.19

changes were not significant compared with baseline values (fig. 2). There were no changes in arterial oxygen saturation.

The paired differences between FAP and non-invasive AP values are shown in tables II–IV. Before exposure, FAP values (systolic, diastolic and mean) were greater (+4, +2, +4 mm Hg) than the corresponding non-invasive AP values in the control group and lower than the non-invasive values (−11, −5, −7 mm Hg) in the patient group. Immediately after exposure, FAP systolic values were significantly less than non-invasive AP values in both groups ($P \leqslant 0.05$). After recovery from the cold exposure (15 and 20 min after exposure), the difference between FAP and non-invasive AP systolic values was significantly greater than during the baseline period ($P \leqslant 0.05$) (fig. 3).

To eliminate the effects of probe displacement on the FAP readings after the exposure, we studied seven other healthy volunteers. FAP was monitored before and after the exposure to cold as in the study groups. The Finapres probes were disconnected during the cold exposure, and were reconnected immediately afterwards. The following day the same persons were exposed to the cold by keeping the right hand in a plastic bag without disconnecting the Finapres probes. On the 3rd day, the same volunteers were again exposed to cold with the right hand in a plastic bag, but the probes were disconnected during the exposure and reconnected thereafter. Finger temperature was 2 (1.5) °C greater in the group of volunteers with their hands in plastic bags and with probes on their fingers than in the other two groups. Greater FAP values (10 mm Hg systolic, 8 mm Hg diastolic and 9 mm Hg mean) after the cold exposure compared with the oscillometric AP values were detected in the group in whom the probes were left on the fingers during the exposure. The differences between FAP and non-invasive AP values between the three groups with probes on and off after the exposure were not statistically significant. Thus the high FAP values were not erroneously caused by displacement of the probe.

DISCUSSION

The aetiology of Raynaud's phenomenon is variable. It may be associated with certain dis-

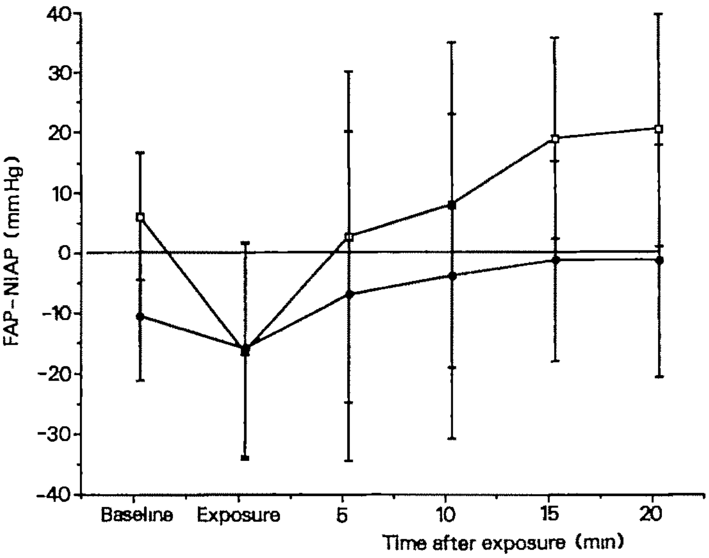

FIG. 3. Mean (SD) differences between the systolic finger arterial pressure (FAP) and non-invasive upper arm arterial pressure (NIAP) in controls (□) and in patients (●) before and after exposure to cold.

eases, chemicals or prolonged exposure to vibration [7]. However, in most individuals Raynaud's phenomenon occurs as an isolated phenomenon. There is no simple and reliable test for the condition, and its true prevalence is difficult to estimate [7–9]. It may not be uncommon, as 22% of the population have a history compatible with Raynaud's phenomenon [13], although this incidence has not been confirmed by others. Thus the influence of Raynaud's phenomenon on non-invasive monitoring devices that are dependent on adequate peripheral circulation is of considerable clinical interest. This study has investigated finger arterial pressure and its relationship to arterial pressure in the upper arm. Cold exposure serves as a model for situations in which vasoconstriction is induced by other factors, such as drugs, increased sympathetic tone or hypovolaemia.

In the present study we examined patients with systemic connective tissue disease with Raynaud's phenomenon and healthy individuals without Raynaud's phenomenon. The responses to cold exposure were similar to those described earlier [9, 10].

FAP was found to be sensitive to cold exposure. In the patient group, FAP values were markedly less than upper arm arterial pressure, probably because of an abrupt increase in vascular tone and even closure of the digital arterioles caused by exposure to cold. A similar phenomenon was described by Olsen and Nielsen [13] using a strain gauge technique to measure finger systolic arterial pressure. In the present study, the response of the control group to cold exposure may be described in two phases. Immediately after exposure, FAP was less than the upper arm pressure. Thereafter, FAP began to increase and exceeded the upper arm pressure significantly 15 min after exposure. A similar phenomenon was described in a previous study in patients with vasoconstriction [3].

There are several possible explanations for the latter phenomenon in our study. First, the Finapres may reflect true finger arterial pressure which is greater than the upper arm pressure after exposure to cold because of increased vascular tone. This phenomenon has been explained by increased pulse wave amplification at the resistance vessels caused by increased peripheral resistance [3].

The high FAP values after cold exposure may be explained also by increased blood volume during the recovery phase in the finger arteries. The software of the Finapres may not be adapted to this situation. The increasing finger blood volume may also cause the probe to become wrapped too tightly round the finger. As a result, the device reads excessive arterial pressures.

In conclusion, in patients with permanent changes in peripheral circulation associated with

Raynaud's phenomenon, the pulsatile flow and volume may be insufficient at times for correct functioning of a finger arterial pressure monitor. In the non-invasive monitoring of finger arterial pressure, the possibility of Raynaud's phenomenon should be considered if a patient has a systemic connective tissue disease or a history of cold intolerance. In these subjects the finger arterial pressure may not always be equal to systemic arterial pressure.

ACKNOWLEDGEMENT

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EFFECT OF MOTION ARTEFACT ON PULSE OXIMETERS: EVALUATION OF FOUR INSTRUMENTS AND FINGER PROBES

J. A. LANGTON AND C. D. HANNING

SUMMARY

The ability of the Ohmeda 3700, Nellcor N200, Datex Satlite Plus and Simed S100 pulse oximeters to detect induced hypoxaemia in the presence of motion artefact was assessed, under conditions of controlled vibration using an industrial vibration facility. Vibration at 4 Hz and 8 Hz induced increases in detection time for hypoxaemia and spurious decreases in the displayed Sa_{O_2} *in some of the oximeters tested. Finger-dependent differences in oximeter performance and pulse rate registration were noted especially in those oximeters without ECG linkage (Ohmeda 3700 and Simed S100). Subsequently, eight different pulse oximeter finger probes were assessed for those characteristics that may predispose to motion artefact. There were marked differences in the mass of the probes, the forces exerted on the test finger and in the force required to displace the probes from the subject's finger. Differences in both the microprocessor programmes and the physical characteristics of the finger probes may explain the observed differences in function. Similar studies should form part of the standard evaluation of new pulse oximeters.*

KEY WORDS

Equipment: pulse oximeters Measurement techniques: pulse oximetry, motion artefact.

The present generation of pulse oximeters suffer from several limitations [1–6]. One major area which has not been explored adequately is that of motion artefact. A recent study [7] produced motion artefact by voluntary finger wiggling. This method cannot be controlled and is not suitable, therefore, for reliable comparisons. In addition, as pulse oximeters are designed to detect hypoxaemia, it is essential that their ability to detect a change in oxyhaemoglobin saturation (Sa_{O_2}) is tested during motion.

The aim of this study was to assess the response of four commercially available pulse oximeters to hypoxaemia whilst the finger–probe interface was subjected to controlled vibration, using an industrial vibration testing facility. Frequencies of vibration were selected to simulate the frequencies that occur in the postoperative period, during recovery from anaesthesia [8].

The results of this study prompted an evaluation of three aspects of finger probe design that may contribute to the development of motion artefact: probe weight, pressure exerted by the probe and force required to displace the probe from the finger. Eight pulse oximeter finger probes from different manufacturers were evaluated.

METHODS

Ethics Committee approval was obtained and all subjects gave informed consent. The study was performed at the Acoustics and Vibration Laboratory, G.E.C. Engineering Research Centre, Whetstone, Leicestershire.

Five healthy male volunteers were studied (mean age 35 yr) resting comfortably in a chair with the left arm placed across the top of the vibration platform and held loosely in a preformed support. The probes of the Ohmeda 3700, Nellcor N200, Datex Satlite Plus and the Simed S100

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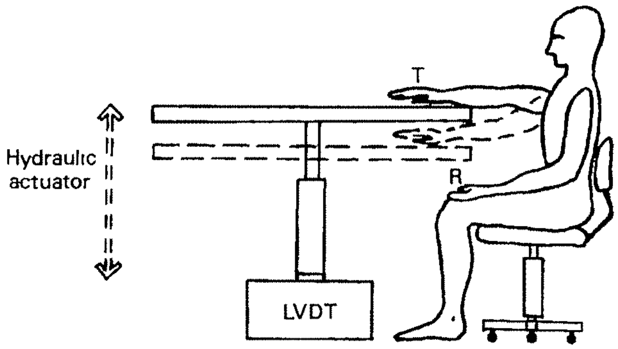

FIG. 1. Diagram of the vibration platform. Hydraulically driven actuator moves table vertically. T = "Test" probes on four fingers of vibrated hand; R = "reference" probes on stationary hand. Motion monitored by LVDT.

pulse oximeters were applied to the fingers of the left hand (excluding the thumb) in a sequence that ensured that every probe was tested on each finger. ECG electrodes were applied in the CM5 configuration and connected to those oximeters with ECG linkage (Nellcor N200 and Datex Satlite Plus). A further probe was applied to the index finger of the right hand for control data and as a safety precaution. The outputs of the oximeters, calibrated according to the manufacturers' instructions, were displayed on a chart recorder. Efforts were made to avoid cooling of the vibrated hand by the application of a fingerless glove.

The platform was vibrated using a vertically mounted, hydraulically driven actuator of 10-t static capability and a maximum stroke of + and −75 mm working at a pressure of 14.7 bar. Frequency and amplitude of vibration were monitored using an LVDT displacement transducer (fig. 1).

Episodes of hypoxaemia were induced by inhalation of 10% oxygen in nitrogen from a prefilled Douglas bag via a closely fitting non-rebreathing mask using normal tidal ventilation. Each episode lasted 2 min or was terminated earlier if the reference instrument indicated that Sa_{O_2} was < 75%. Episodes were separated by a 3-min recovery period during which the subject breathed room air. Detection time was defined as the time from the first breath of 10% oxygen to the first sustained decrease of > 2% in Sa_{O_2} and was obtained from the permanent record. The minimum Sa_{O_2} attained with each episode of hypoxaemia was compared for each finger with the pre-vibration control value. Pulse rate discrepancies were defined as a difference of > 20 beat min^{-1} compared with that derived from the ECG. Preliminary testing showed that a spurious decrease in displayed Sa_{O_2} could be induced by vibration alone in some instruments. A significant decrease was defined as > 5% from the control value

A 5-min period of breathing room air during which baseline readings were recorded was followed by two episodes of hypoxaemia. Sinewave vibration was commenced at 4 Hz at an amplitude of + and −12.5 mm and, after a 2-min period of observation of the effects of vibration, two episodes of hypoxaemia were induced as before whilst vibration continued. The sequence was repeated with each probe applied to each finger.

The complete sequence was repeated using intermittent bursts of vibration at 8 Hz square wave applied for 5 s on and 5 s off. In the second part of the study, eight pulse oximeter finger probes were evaluated on a laboratory model and on five normal volunteers (three male). The weight of the probe was determined by weighing the probe, lead and connector on a Harvard trip balance and then supporting the probe so that the weight of the lead and connector were determined, and subtracting one from the other. The probe was applied to a pressure sensor constructed from a water-filled finger from a surgical glove connected to a manometer tube. The change in the height of the water meniscus was taken as an indication of the pressure exerted by the probe.

The force required to displace the oximeter probe from each of the subject's fingers was assessed. The subject was seated with the left hand secured to the preformed arm support. The finger probe was attached by a thread, through a pulley, to a plastic container of known weight.

The finger was elevated slightly to prevent the probe catching on the work surface and water was added to the container until the probe was displaced. The total weight required was recorded. This was repeated twice on each finger of each subject.

The volume of each subject's hand and fingers was measured by displacement of water. The hand volume was defined as the volume of water displaced by immersion up to a line drawn across the wrist at the level of the ulnar styloid. The finger volume was measured by immersion up to the metacarpal–phalangeal joints. The finger volume was calculated also from the mean of the antero–posterior and lateral dimensions of each finger at the distal and proximal interphalangeal joints and the distance between the tip of the finger and the proximal interphalangeal joint. It was assumed that the finger approximated to a cylinder.

Analysis of data

The performance of each instrument was compared for each finger using each instrument as its own control. Data were analysed statistically using the Wilcoxon signed rank test and the McNemar test for matched samples. Detection time and control values were compared by analysis of variance. Statistical significance was assumed if $P < 0.05$.

RESULTS

Detection time

A significantly prolonged detection time was noted at 4 Hz sinewave vibration (table I) for the Ohmeda 3700 with the probe on the index, ring and little fingers ($P < 0.05$). The Simed oximeter had a significantly prolonged detection time on the index and middle fingers, but not on any of the other fingers ($P < 0.05$). No reliable values for Sa_{O_2} could be obtained with the Satlite Plus when the probe was placed on the little finger.

The 8-Hz intermittent vibration (table II) induced significantly longer detection times for the Ohmeda 3700 when the probe was applied to the index, ring and little fingers ($P < 0.05$). The Simed oximeter also demonstrated increased detection times when the probes were on the index, middle and little fingers ($P < 0.05$). The Satlite Plus showed significantly prolonged detection times when applied to the index and little fingers ($P < 0.05$).

There were no significant differences between the instruments in control detection times on any finger. The detection time at 4 Hz for the Ohmeda

TABLE I. *Detection time and minimum Sa_{O_2} (Satn) for induced hypoxaemia for each instrument under control conditions and at 4-Hz continuous sine wave vibration (mean (SEM)).* n = 5. *P < *0.05 compared with own control.* †*Data not amenable to interpretation*

	Control		4 Hz	
Instrument	Time (s)	Satn (%)	Time (s)	Satn (%)
Index finger				
Ohmeda 3700	27.7 (1.2)	79.3 (2.5)	42.7 (6.6)*	81.2 (2.6)
Nellcor N200	33 6 (3.3)	81.3 (2.8)	39 3 (4 7)	80.0 (3.7)
Datex Satlite Plus	27.6 (2.5)	83.4 (1.8)	40.8 (4.7)	84.2 (2.8)
Simed S100	28.6 (2.2)	84.7 (1 7)	54 2 (10.4)*	85.6 (1.5)
Middle finger				
Ohmeda 3700	27.7 (1 2)	79 6 (2.5)	42.7 (6.4)	81 0 (3.0)
Nellcor N200	34.1 (2.9)	80.3 (2.8)	36.0 (2.1)	85.5 (1.4)
Datex Satlite Plus	28.5 (2 4)	84 6 (1.9)	29.8 (1.6)	80.7 (2.2)
Simed S100	29 5 (2.3)	82 8 (2.1)	42.7 (4.7)*	85.4 (2.2)
Ring finger				
Ohmeda 3700	29.0 (1.0)	79.3 (2.5)	49.9 (5.4)*	81.1 (3.1)
Nellcor N200	34.5 (2.9)	80.6 (2 8)	35.5 (3.3)	83.4 (2.3)
Datex Satlite Plus	27.6 (2.5)	82 8 (1.9)	32.6 (3.9)	80.4 (3.1)
Simed S100	29.5 (2.3)	82.8 (2.3)	38.9 (7.2)	81 6 (2.4)
Little finger				
Ohmeda 3700	27.2 (1.2)	80.3 (2.5)	49.9 (4.9)*	81.1 (3.1)
Nellcor N200	33.6 (3.3)	81.3 (2.8)	42.5 (4.0)	84.8 (1.9)
Datex Satlite Plus	†	†	†	†
Simed S100	29 0 (2.2)	84.7 (1.7)	33.6 (2.7)	82.3 (3.4)

TABLE II. *Detection time and minimum* Sa_{O_2} *(Satn) for induced hypoxaemia for each instrument under control conditions and at 8-Hz square wave intermittent burst vibration (mean (SEM)), n = 5.* $^*P < 0.05$ *compared with own control*

Instrument	Control Time (s)	Control Satn (%)	8 Hz Time (s)	8 Hz Satn (%)
Index finger				
Ohmeda 3700	27.7 (0.9)	79.5 (2.5)	46.1 (5.2)*	83.8 (3.5)
Nellcor N200	33.7 (2.7)	81.3 (2.8)	37.4 (2.8)	82.5 (4.5)
Datex Satlite Plus	28.3 (2.4)	84.9 (2.0)	40.3 (1.9)*	87.2 (2.2)
Simed S100	30.0 (2.0)	84.7 (1.7)	50.9 (7.2)*	85.4 (1.8)
Middle finger				
Ohmeda 3700	27.7 (0.9)	79.8 (2.5)	42.2 (6.9)	80.8 (3.2)
Nellcor N200	33.2 (3.1)	80.6 (2.8)	36.5 (3.6)	84.4 (2.9)
Datex Satlite Plus	29.3 (2.7)	83.9 (2.1)	36.5 (3.3)	85.2 (2.4)
Simed S100	31.7 (0.9)	84.3 (1.8)	46.1 (2.9)*	85.5 (1.5)
Ring finger				
Ohmeda 3700	28.2 (1.2)	80.5 (2.5)	50.9 (5.4)*	84.3 (2.3)
Nellcor N200	35.0 (2.5)	85.4 (1.7)	42.2 (6.7)	82.8 (2.7)
Datex Satlite Plus	28.7 (2.1)	83.8 (3.5)	38.4 (5.0)	84.2 (2.7)
Simed S100	30.2 (2.2)	84.7 (1.7)	46.1 (7.7)	85.2 (2.4)
Little finger				
Ohmeda 3700	27.1 (0.9)	78.5 (2.5)	48.1 (3.4)*	77.5 (2.6)
Nellcor N200	33.2 (3.1)	81.6 (2.7)	40.3 (2.4)	86.6 (2.0)
Datex Satlite Plus	28.7 (2.1)	84.9 (2.1)	38.4 (4.6)*	82.8 (2.4)
Simed S100	29.8 (2.2)	83.8 (3.6)	45.1 (3.3)*	80.5 (4.8)

TABLE III. *Pulse rate discrepancies (> 20 beat* min^{-1} *difference from ECG) and mean (SEM) [range] reduction in* Sa_{O_2} *reading on starting vibration but before breathing hypoxic mixture, at 4-Hz sinewave vibration and at 8-Hz intermittent vibration.* n = 5. $^*P < 0.05$; $^{**}P < 0.01$ *(McNemar's test)*

Instrument	Non-vibrated	4 Hz	8 Hz
Pulse rate discrepancies			
Ohmeda 3700	0/20	17/20**	1/20
Nellcor N200	0/20	4/20	0/20
Datex Satlite Plus	0/20	1/20	1/20
Simed S100	0/20	9/20**	0/20
Mean Sa_{O_2} (%)			
Ohmeda 3700	95.9 (0.2) [94–97]	90.6 (0.3)* [87–94]	91.2 (0.7)* [79–96]
Nellcor N200	96.8 (0.3) [95–100]	95.9 (0.5) [89–98]	96.6 (0.2) [95–98]
Datex Satlite Plus	96.7 (0.2) [95–98]	95.0 (0.5)* [88–97]	95.1 (0.4)* [90–97]
Simed S100	97.5 (0.3) [96–100]	93.0 (0.6)* [88–97]	92.7 (0.7)* [81–97]

3700 applied to the little finger was significantly longer than that of the other oximeters ($P < 0.05$).

Minimum saturation

Generally, there were no significant differences in the minimum Sa_{O_2} detected during vibration by the instruments compared with their own control values and when compared with the Biox III oximeter on the non-vibrated hand. The exception to this was the Nellcor N200 at 4 Hz and 8 Hz, which gave significantly greater minimum values when applied to the little finger ($P < 0.05$). There were no significant differences between instruments with respect to both the control and test minimum Sa_{O_2} values.

Pulse rate discrepancies (table III)

The 4-Hz sinewave vibration induced signifi-

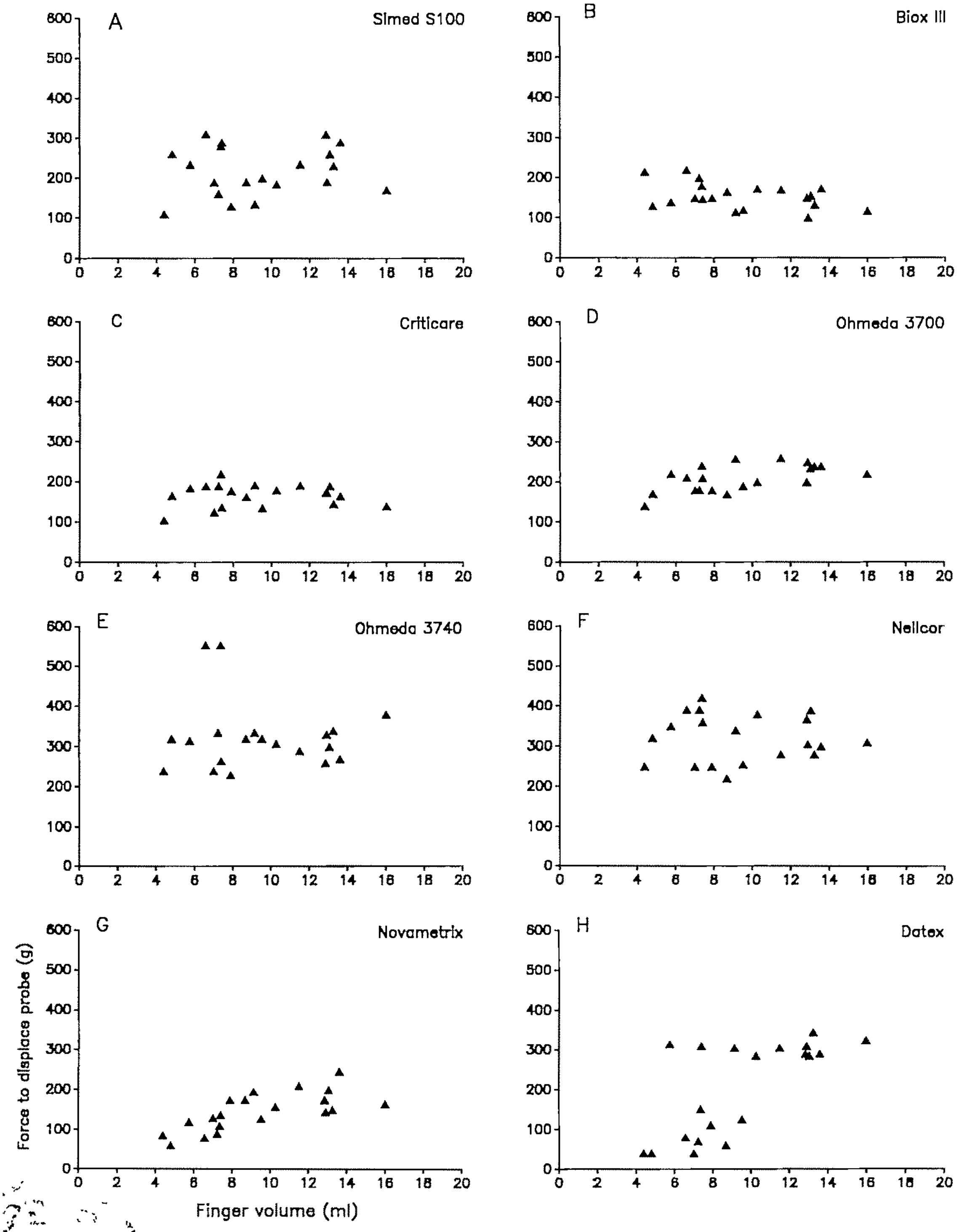

FIG. 2. Force of displacement of finger probes plotted against subject finger volume for eight pulse oximeters. (Labels on graph G apply to all other graphs.)

cant ($P < 0.01$) pulse rate discrepancies in the Ohmeda 3700 and Simed S100 oximeters. There were no significant pulse rate discrepancies in any of the oximeters during the 8-Hz intermittent vibration.

Spurious decreases in Sa_{O_2}

A significant decrease in displayed Sa_{O_2} occurred on starting the vibration sequences with the Ohmeda 3700, Simed S100 and Satlite Plus oximeters. This occurred on starting the vibration before the subject breathed the hypoxic mixture, and generally persisted until the vibration ceased.

Laboratory testing

The three male subjects had measured mean hand and finger volumes of 423 and 123 ml, respectively. The corresponding values for the two female subjects were 227 and 43.5 ml.

There was a nearly three-fold variation in the weight of the finger probes and a similar variation in the pressure exerted by the probes on the pressure sensor.

In general, more force was required to displace the probes from the index and middle fingers than from the ring and little fingers. The forces were in the range 40–553 g. The displacement force was plotted against calculated finger volume for each probe (fig. 2A–H).

The probes appeared to fall into three groups:
(a) Those with a displacement force of approximately 250–300 g which did not vary with finger volume (Nellcor and Ohmeda 3740).
(b) Those with a displacement force of 150–250 g which did not vary with finger volume (Simed, Ohmeda 3700, Criticare, Biox III).
(c) Those where the force varied with finger volume. In the case of the Novametrix a clear linear relationship existed, but it was less clear for the Satlite, with which the force was approximately 300 g for male fingers but < 150g for female.

DISCUSSION

During recovery from anaesthesia, in intensive care and other situations, the finger–probe interface may be subject to vibration and it is important that the performance of pulse oximeters in these situations is known.

Vibration was found to interfere with pulse oximeter function, producing a prolongation in the detection time for hypoxaemia without necessarily giving a warning. Vibration also produced spurious decreases in the displayed Sa_{O_2} which often persisted until the vibration ceased.

Sine wave vibration was chosen in order to produce regular, cyclical vibration that would produce regular motion artefact and therefore interfere with pulse oximeter software. This emphasized the importance of waveform display on the oximeter, as the artefactual nature of the pulse wave could be seen easily.

The pulse oximeters that possess ECG linkage seemed to perform better in this study, but this merits further investigation. There were finger-dependent differences, producing a greater incidence of motion artefact on the smaller fingers. This finding should be noted for future studies of motion artefact.

The two types of vibration used in this study were chosen to simulate vibration that may be encountered in clinical practice: the 4-Hz sine-wave was used to simulate postoperative recovery and the 8-Hz square wave intermittent bursts were to mimic conditions that may be produced during transport of patients.

The physical characteristics of the finger probes (table IV) showed that there are wide variations in

TABLE IV. *Physical properties of oximeter finger probes. †See text for derivation*

Probe	Weight (g)	Pressure exerted†	Lining material	Spring
Ohmeda 3700	17.7	33	No lining material: smooth plastic	Metallic
Datex Satlite Plus	28.7	53	White rubber	Metallic
Nellcor N200	36	46	White rubber	Metallic
Simed S100	26	48	Smooth plastic	Metallic
Ohmeda 3740	19	42	Black rubber	Metallic
Criticare	27	22	Smooth rubber; only one surface	Metallic
Novametrix	16.3	29	Soft rubber	Plastic
Biox III	46.5	48	No lining material	Metallic

the mass of the probes and in the force that they exert on the test finger. The force required to displace the finger probes from the subjects' fingers demonstrated that some probes required a consistent force for displacement, while others required only small forces to displace them from small volume fingers.

The finger probes that performed "well" had several common characteristics. These probes were lined with soft material that minimized movement of the finger–probe interface; they also exerted some of the highest pressures on the test finger. Other factors that should be considered include mass of probe and mechanics of the spring mechanism by which the probes grip the finger.

We conclude that the complex factors involved in production of motion artefact do not permit recommendation of any one instrument–probe combination. Our study has highlighted some of the effects of vibration on pulse oximeter function and it has outlined some of the desirable features in probe design which may help to reduce the generation of motion artefact.

ACKNOWLEDGEMENTS

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

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EFFECT OF NITROUS OXIDE SEDATION ON THE VENTILATORY RESPONSE DURING HYPOCAPNIA

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Previous investigators have shown that following a period of hyperventilation, breathing either air or a nitrous oxide mixture, there was a period of hypoxaemia which was significantly greater after nitrous oxide [1]. It was postulated that this was the result of the effect of nitrous oxide on (1) ventilatory drive; (2) ventilatory response to hypoxia; (3) V/Q mismatch; or (4) diffusion hypoxia. We examined the hypothesis that this was entirely the result of the effect of nitrous oxide on ventilatory control when the subject was below the "apnoeic threshold". Oxygen saturation (Sa_{O_2}) was recorded with an Ohmeda Biox 3700 pulse oximeter and inspired and end-tidal gases measured using a mass spectrometer (Ohmeda 6000). The output from these instruments was analysed by computer. Variables obtained were breath number, ventilatory frequency, inspiratory and expiratory tidal volumes and minute ventilation; inspired and end-tidal concentrations of nitrogen, oxygen, carbon dioxide and nitrous oxide. Real and elapsed time were recorded.

Six normal volunteers gave informed consent and were familiarized with the apparatus; each breathed through a Fleisch pneumotachograph. The study was divided into three parts carried out randomly on different days as follows: hyperventilation breathing air to an end-tidal carbon dioxide of 3 kPa for 2 min followed by 90 s hyperventilating with either air or a 75 % nitrous oxide in oxygen mixture. At the end of the hyperventilation period the subject was told to relax completely whilst breathing room air and changes in Sa_{O_2} and ventilation were measured continuously. In the third part of the study the ventilation–carbon dioxide response curve was measured in quasi-steady state manner to derive the apnoeic threshold. Figure 1 shows (A) resting ventilation at the start

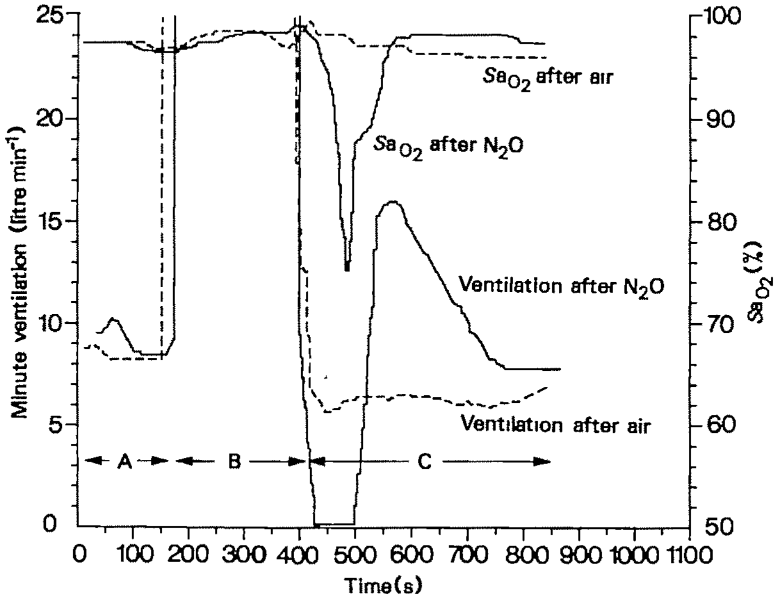

FIG. 1. Changes in ventilation and oxygen saturation (Sa_{O_2}) following nitrous oxide (N_2O) or air breathing in one subject.

of the study; (B) the period of hyperventilation; and (C) the changes in Sa_{O_2} and ventilation following nitrous oxide or air breathing in one subject.

The mean apnoeic threshold was 5.2 kPa and the mean PE_{CO_2} on the first breath following apnoea was 4.4 kPa. Five of the six subjects became apnoeic (29–130s) following nitrous oxide but no subject became apnoeic following air breathing. The lowest mean Sa_{O_2} following nitrous oxide was 75% and the lowest mean Sa_{O_2} following air was 92.5%. This is a significant difference at the 0.05 level.

Apnoea is the predominant factor explaining desaturation following hyperventilation with nitrous oxide when PE_{CO_2} is below the apnoeic threshold.

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LATE POSTOPERATIVE EPISODIC AND CONSTANT HYPOXAEMIA AND ASSOCIATED ECG ABNORMALITIES

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PREOPERATIVE OVERNIGHT PULSE OXIMETRY AS A PREDICTOR OF PULMONARY COMPLICATIONS AFTER MAJOR VASCULAR SURGERY

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There is current interest in the role of preoperative assessment of respiratory function as a predictor of postoperative respiratory complications [1]. Therefore, we analysed data from 17 patients undergoing major abdominal vascular surgery to test whether the mean preoperative overnight (sleeping) saturation (Sa_{O_2}) value correlated with Sa_{O_2} values on the third and fifth nights after operation (both measured in the absence of added oxygen). Also we wanted to ascertain the value of Sa_{O_2} measurements in identifying patients most likely to be at risk of developing postoperative pulmonary complications.

Data points for Sa_{O_2} were sampled overnight, once every second using an Ohmeda 3700 pulse oximeter, and then transferred into a portable computer. Analysis was performed using a programme designed for respiratory sleep studies, giving the mean overall Sa_{O_2} for each night and also a preoperative mean Sa_{O_2} value over a 30-min period whilst the patient was awake. All patients received a standardized general anaesthetic technique. No patient received extradural analgesia. Postoperative analgesia was i.m. papaveretum 15–20 mg every 4 h, as required. Serious pulmonary complications were defined as a need for re-ventilation because of respiratory failure (two patients), or where medical notes reported the presence of postoperative atelectasis or infection on the basis of either sputum culture (one patient), a change in antibiotic therapy (one patient), or extra nebulizers and physiotherapy being prescribed (three patients).

TABLE I. *Preoperative overnight (sleeping) Sa_{O_2} values as a predictor of likely pulmonary complications*

Variables	Likelihood of chest complications (*P* value)
Mean overnight sleeping Sa_{O_2} Preop $<94\%$ ($n = 11$)	0.0065
Preop FEV_1/FVC ratio $<68\%$ ($n = 13$)	0.03
Patients with both abnormal Sa_{O_2} and FEV_1/FVC ratio ($n = 8$)	0.00015

Mean preoperative Sa_{O_2} values recorded during sleep (range 92.8–97.5%) correlated well with saturation values obtained after operation on nights 3 and 5 ($P < 0.001$; *r* values 0.92 and 0.80, respectively). There was a weak correlation between the preoperative awake 30-min value and Sa_{O_2} on night 5 ($P < 0.01$; *r* value 0.63). Mean preoperative overnight sleeping saturation and spirometric values (variables) as a means of identifying patients at risk of pulmonary complications were assessed by the Fisher exact test (table I).

Patients with mean preoperative overnight Sa_{O_2} values of $<94\%$ appeared to be at risk of postoperative respiratory complications. The FEV_1/FVC ratio was not as sensitive a predictor. However, the combination of a reduced FEV_1/FVC ratio and a preoperative saturation value during sleep of $<94\%$ increased the predictive value of assessing those at risk. Only one of the eight patients with both risk factors had an uncomplicated postoperative pulmonary recovery. The significant relationship between the preoperative sleeping Sa_{O_2} value and the Sa_{O_2} values subsequently achieved on nights 3 and 5 suggested that the use of overnight oximetry may be helpful in identifying, pre-emptively, patients at risk of developing pulmonary complications.

ACKNOWLEDGEMENT

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RESPONSE TIME OF PULSE OXIMETERS TO RAPID CHANGES IN SATURATION

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The accuracy of pulse oximeters has been investigated extensively, but less attention has been paid to the response times of these machines. To measure the response time of an oximeter. The arterial saturation must be changed as rapidly as possible. The ideal is an instantaneous step from one satu-

TABLE II. *Mean relative response times for 11 finger probes*

Machine	Mean relative response time (s)	SD
Kontron 7840	−9.0	12.6
Minolta Pulsox-7	22.7	18.0
Physiocontrol	6.0	15.8
Critikon Oxyshuttle	29.4	27.5
Novametrix 515	−0.4	23.9
Datex Satlite	−6.7	14.0
Datascope Accusat	−7.4	13.2
Nonin 8604	−10.2	13.3
Ohmeda 3700	−6.2	16.8
Ohmeda 3740	−8.0	13.9
Nelcor N200	−4.0	14.4

ration to another. Severinghaus produced rapid changes in saturation using inhaled hypoxic gas mixtures [1] but a more rapid change can be produced by acutely changing barometric pressure. We investigated the response time of 11 different pulse oximeters (21 probes) to a step change in arterial saturation produced by acute decompression.

The study was performed in the hypobaric chamber at the RAF Institute of Aviation Medicine. Eleven subjects were decompressed a total of 20 times from an ambient pressure of 565 to 380 mm Hg over 3 s. This produced an acute decrease in arterial saturation of 10%. Each subject had 11 oximeters attached, nine finger probes and two ear probes. All oximeters were set at their shortest averaging time.

The time for each oximeter reading to decrease by 5 and 10% was recorded. To eliminate the effect of lung–finger circulation time, the results for all the oximeters on the fingers of any one subject were averaged and the response times for each oximeter expressed as the difference from this mean. For each machine these differences were averaged for all 20 decompressions to give the mean relative response time for the oximeter.

Table II shows the results for the mean relative response times for finger probes for a 10% decrease in saturation. The oximeters have similar response times except for the Minolta Pulsox and the Critikon Oxyshuttle which were slower. The difference in response times is probably a result of different signal processing algorithms in the software of the oximeter.

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EFFECTS OF AMINOPHYLLINE ON THE ISOLATED RAT PHRENIC NERVE–HEMIDIAPHRAGM PREPARATION ARE POTENTIATED BY HALOTHANE AND ISOFLURANE

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It has been shown that aminophylline stimulates diaphragmatic contractility [1] while volatile anaesthetic agents are generally depressants [2]. However, little is known of their action in combination.

We studied the effect of aminophylline in the presence of halothane or isoflurane on the isolated rat hemidiaphragm preparation. Male Sprague-Dawley rats were decapitated under ether anaesthesia and the left phrenic nerve–hemidiaphragm was transferred to a tissue bath containing Tyrode's solution with double (11.1 mmol $litre^{-1}$) glucose. The preparation was aerated with 95% oxygen and 5% carbon dioxide and maintained at 37 °C, pH 7.40. The tissue was mounted under isometric conditions using Grass FT03C transducers. After equilibration, a resting tension of 2 *g* was set on the diaphragm and the nerve was stimulated using a Grass S88 stimulator (0.12 Hz, 0.1 ms duration, supramaximal voltage). Tension was displayed on a calibrated chart recorder. The results were analysed using Student's *t* test and Duncan's multiple range test.

A dose–response curve was determined for aminophylline alone, then 1 MAC halothane or 1 MAC isoflurane was added to the aerating mixture and the aminophylline dose–response curve repeated. Gas chromatography confirmed that steady state concentrations of the volatile agents in the solution were achieved.

Neither 1 MAC halothane nor 1 MAC isoflurane alone had any significant effect on the response of the preparation. Aminophylline alone increased resting and twitch tension in a dose-dependent manner. The addition of 1 MAC halothane in the presence of aminophylline produced a further significant increase in resting and twitch tension. The increase in twitch tension could be accounted for almost entirely by the increase in resting tension. These effects were also seen with isoflurane but with greater doses of aminophylline.

Tubocurarine 2×10^{-6} mol $litre^{-1}$ did not abolish the increase in resting tension with aminophylline and halothane, but dantrolene 1.88×10^{-6} mol $litre^{-1}$–3.76×10^{-6} mol $litre^{-1}$) almost completely attenuated the increase. This concentration of dantrolene had little effect on the resting tension. This observation suggests that the potentiation of the action of aminophylline by halothane is caused by intracellular calcium release.

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MAC REDUCTION OF DESFLURANE WITH FENTANYL: COMPARISON WITH ISOFLURANE

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Desflurane is a new volatile anaesthetic agent currently undergoing clinical investigation in man [1]. The blood/gas partition coefficient of desflurane is 0.42 and thus rapid induction of and recovery from anaesthesia with this agent should occur. The MAC of desflurane is 7.25% (in patients aged 18–30 yr) or 6% (in patients aged 31–65 yr) [2]. Since desflurane will be used commonly with an opioid such as fentanyl, this study was undertaken to determine the MAC reduction produced by two different doses of fentanyl and to

TABLE III. *Details of patients, anaesthesia and measurements of MAC. Des = Desflurane; Iso = Isoflurane*

Anaesthetic	Des	Des	Des	Des	Des	Iso	Iso
Fentanyl (μg kg^{-1})	0	3	3	6	6	3	3
Age (yr)	31–65	18–30	31–65	18–30	31–65	18–30	31–65
MAC (%)	6.20	2.56	3.22	2.35	2.25	0.68	0.61
SD	0.37	0.45	0.71	0.22	0.96	0.08	0.09
MAC reduction (%)	0	66	48	68	64	47	45

compare this with the MAC reduction obtained using these doses of fentanyl with isoflurane using the "up–down" method [3].

One hundred and thirty-four unpremedicated adults, ASA I or II, (age 39 (SD 13) yr, weight 78 (SD 14.7) kg) gave informed consent for the study. Patients were stratified by age and allocated randomly to five groups: desflurane–oxygen, desflurane–oxygen–fentanyl 3 μg kg^{-1}, desflurane–oxygen–fentanyl 6 μg kg^{-1}, isoflurane–oxygen–fentanyl 3 μg kg^{-1}, isoflurane–oxygen–fentanyl 6 μg kg^{-1}. The appropriate dose of fentanyl was given, followed by thiopentone 3–5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1}. Patients then received either desflurane or isoflurane in oxygen. Following tracheal intubation, end-tidal agent concentration was adjusted to 1.0 MAC (no fentanyl), 0.8 MAC (fentanyl 3 μg kg^{-1}) or 0.6 MAC (fentanyl 6 μg kg^{-1}). Measurement of change in MAC in the 60 s succeeding incision was made and the patient given an increase (move) or decrease (no move) of 10 % MAC end-tidal agent concentration.

Satisfactory MAC determinations were not made in the isoflurane–oxygen–fentanyl 6 μg kg^{-1} group because of the inability to adjust agent concentrations satisfactorily in the 0.2 % end-tidal range for isoflurane. Time to opening was significantly faster in the desflurane–oxygen–fentanyl 3 μg kg^{-1} younger group than in the 6 μg kg^{-1} older group.

The MAC value of 6.2 % obtained for the thiopentone induction with desflurane–oxygen in the 31–65 yr age group (table III) is very similar to the 6 % obtained using gas induction [2] Although desflurane is a less potent agent than isoflurane the interaction with fentanyl appears to be similar in terms of MAC reduction. It is also associated with faster recovery.

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EFFECT OF 5 % AND 10 % MAC OF NITROUS OXIDE AND ISOFLURANE ON PEAK VELOCITY OF SACCADIC EYE MOVEMENTS

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EFFECT OF PROLONGED SEDATION WITH ISOFLURANE ON PLASMA FLUORIDE CONCENTRATIONS IN CRITICALLY ILL PATIENTS

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Subanaesthetic concentrations of isoflurane have been used to sedate ventilated patients in the intensive therapy unit (ITU) [1]. Isoflurane is metabolized only minimally (0.2%) and sedation for a mean period of 18 h produces an insignificant increase in plasma fluoride concentration [2]. Fluoride-induced nephrotoxicity manifests initially as an inability to concentrate urine and is generally associated with peak plasma concentrations > 50 μmol litre^{-1}. We investigated the effect of prolonged isoflurane sedation on plasma fluoride concentrations.

Fifty-six patients admitted to the ITU, who were expected to require ventilation for longer than 24 h, were allocated randomly to receive either 0.1–0.6% isoflurane (group 1) or midazolam 0.01–0.2 mg kg^{-1} h^{-1} (group 2). Plasma concentrations of inorganic fluoride were measured in all patients before sedation, regularly during the period of sedation and for a week afterwards, using an ion-selective electrode technique. Table IV summarizes the results. In both groups the mean baseline plasma concentration of fluoride (i.e. on admission to the ITU) was within the normal range but the scatter was very wide, possibly as a result of the long anaesthesia before ITU admission. In group 1 there was a gradual increase in plasma concentrations of fluoride with time, which reached a peak 16 h after sedation and decayed exponentially to reach normal concentrations by the fourth day. The maximum concentration of fluoride correlated with the total MAC

TABLE IV. *Plasma fluoride concentrations (F^-) (μmol litre^{-1}) at baseline (Base), at 12 h, at the end of sedation (End) and the maximum concentration (Max) seen with isoflurane (group 1) and midazolam (group 2). Mean (range), N/A = not applicable*

	Group 1 (n = 28)	Group 2 (n = 28)
Duration (h)	37.75 (8–127)	39.12 (4–104)
MAC h	9.76 (1.1–34.4)	N/A
Base F^-	5.92 (0.6–54.1)	5.13 (1.1–21.0)
12 h F^-	8.23 (1.3–21.7)	8.44 (1.4–41.7)
End F^-	17.49 (2.9–76.0)	6.48 (1.2–18.2)
Max F^-	24.60 (2.8–81.6)	8.44 (1.4–41.7)

hours of isoflurane but was independent of renal function. In group 2 the mean concentration of fluoride increased to reach a peak after 12 h of sedation and then returned to normal. This supports previous work that plasma concentrations of fluoride continue to increase after anaesthesia [3].

Renal function, as assessed by serum electrolytes, urea and creatinine concentrations, creatinine clearance and urine output rates, and osmolality were similar in the two groups.

The plasma inorganic concentrations of fluoride are the highest documented in humans following isoflurane administration. Despite the high peaks obtained, no clinical deterioration of renal function was observed.

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OESOPHAGEAL CONTRACTILITY DURING TOTAL I.V. ANAESTHESIA

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Dose requirements for infusion of propofol in combination with alfentanil have recently been established using somatic motor responses as the index of anaesthesia [1]. It is thought that visceral motor responses such as spontaneous or provoked lower oesophageal concentrations (SLOC and PLOC) may also be useful as an index of anaesthesia [2]. We have determined the dose requirements of propofol for abolishing these visceral motor responses in patients undergoing body surface surgery under general anaesthesia.

Fifty healthy patients were premedicated with temazepam 20–30 mg 2 h before anaesthesia. Patients were allocated randomly to one of five groups, A to E. In group A anaesthesia was induced with alfentanil 50 µg kg^{-1} and propofol 1 mg kg^{-1} and maintained with infusions of alfentanil 50 µg kg^{-1} h^{-1} and propofol 10 mg kg^{-1} h^{-1} for 10 min, 8 mg kg^{-1} h^{-1} for 10 min and 6 mg kg^{-1} h^{-1} subsequently. Patients in groups B to E were treated in the same way except that the propofol infusions were reduced to 75%, 60%, 50% and 40% of those used in group A. Suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation and passage of a Lectron oesophageal motility probe. Ventilation was continued with oxygen-enriched air (FI_{O_2} = 0.3), to produce an end-tidal PE'_{CO_2} of 4.8–5.2 kPa. Spontaneous return of neuromuscular function was confirmed before the beginning of surgery. At incision, the patient's motor response was noted as either movement or no movement. Presence of SLOC and PLOC was noted. Venous blood was obtained for measurement of whole blood propofol concentration. If the patient moved at any time following incision, further increments of propofol 20 mg were given.

Probit analysis of the ratio of movers to non-movers at incision revealed an ED_{50} (95% confidence limits) of 2.5 (1.8–2.9) mg kg^{-1} h^{-1} and ED_{95} (95% confidence limits) of 4.7 (4.0–7 5) mg kg^{-1} h^{-1} for somatic movement. Venous blood concentrations gave an EC_{50} value of 1.2 (0.4–1 6) µg ml^{-1} and an EC_{95} of 4.0 (2 8–18.5) µg ml^{-1}. ED_{50} (95% confidence limits) of propofol for preventing SLOC was 3.0 (1.9–3.6) mg kg^{-1} h^{-1}, ED_{95} (95% confidence limits) was 6 9 (5.0–27 3) mg kg^{-1} h^{-1}; EC_{50} was 1.7 (0.7–2.3) µg ml^{-1} and EC_{95} was 5 9 (3 7–70.6) µg ml^{-1}.

The log–dose probit response curves for somatic movement and SLOC were parallel, with the SLOC curve to the right of that for somatic movement. The curve for PLOC was more shallow and to the left of the SLOC and somatic movement curves.

A further 10 patients were given glycopyrrolate 5 µg kg^{-1} at induction and otherwise treated as though they were in group D; oesophageal contractility was reduced significantly in this group.

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INCIDENCE OF RECALL OF AWARENESS DURING ANAESTHESIA FOR NON-OBSTETRIC SURGERY

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Awareness is an emotive subject which has attracted much recent publicity and medico–legal interest. The true incidence of awareness with recall in general anaesthetic practice is uncertain. Reported incidences vary widely, partly because of differences in methodology. Jelicic and Bonke [1] suggested that a structured interview is necessary when seeking evidence of awareness. The last reported study which used a structured postoperative interview was in 1975 [2]. The most recent report in the literature concentrated solely on obstetric patients, in whom the incidence of awareness is likely to be greatest. Many new anaesthetic drugs have come into clinical use since 1975. We therefore embarked on a structured postoperative interview study of 1000 patients to determine the incidence of awareness, defined as recall of events during anaesthesia, in general anaesthetic practice.

Patients younger than 16 yr, those who had undergone obstetric or intracranial surgery, patients with mental confusion or no knowledge of the English language and patients discharged from hospital before the postoperative visit were not interviewed. All patients were interviewed between 20 and 36 h after surgery by one of three anaesthetists, each of whom used the same questions. Patients were not told the purpose of the investigation until after the interview. At the same visit the anaesthetic records were scrutinized and the drugs, techniques and any comments made by the anaesthetists were recorded. None of the anaesthetists in the hospital (other than the authors) knew that the study was being undertaken. This was to ensure that their anaesthetic practice was not altered.

One thousand patients were interviewed between February and April 1990. Of these, 316 breathed spontaneously through the procedure (group A), 92 received suxamethonium to facilitate tracheal intubation only (group B), and 592 received neuromuscular blocking agents and positive pressure ventilation throughout surgery (group C). Two patients (0.2%) remembered events during anaesthesia: one patient in group B had some recall of tracheal intubation and one patient in group C remembered events after tracheal intubation, but before surgery. Neither patient experienced pain and neither was distressed.

The incidence of awareness with recall in this study was 0.2% (95% confidence intervals 0.7%–0.02%) and is lower than in previous reported studies [3]. This lower incidence may be attributable to changes in technique among anaesthetists. Both our cases of awareness occurred shortly after induction and were related to a low induction dose: patient weight ratio. More care may be required in determining doses of induction agents before administration of neuromuscular blocking drugs.

ACKNOWLEDGEMENT

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MIDAZOLAM-INDUCED AMNESIA, SEDATION AND PSYCHOMOTOR IMPAIRMENT: A DOSE RESPONSE STUDY

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POSTOPERATIVE PCA WITH ALFENTANIL: EFFICACY OF BACKGROUND INFUSIONS

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The use of alfentanil as a suitable agent for postoperative analgesia has been reported previously [1]. It was suggested that improved analgesia might be obtained by a background infusion accompanied by suitable bolus demands. This study was designed to compare the efficacy and safety of such an infusion plus demand regimen with "pure" PCA.

Forty patients received a standardized anaesthetic using alfentanil as the sole opioid. After operation each patient was assigned randomly to receive either bolus doses of 200 μg or 300 μg, a background infusion of 900 $\mu g\ h^{-1}$ plus bolus doses of 100 μg and a background infusion of 900 $\mu g\ h^{-1}$ with bolus doses of 200 μg. The lockout interval was 5 min in all groups. Measurements of pain score (VAS), sedation score, ventilatory frequency, heart rate and arterial pressure were made every hour throughout the 24 h of the study. Whole blood alfentanil concentrations were measured for each patient using solvent extraction and GLC-NPD.

Fifteen patients were withdrawn from the study, eight because of inadequate analgesia; six of these patients were in the pure PCA group and two were in the infusion plus PCA groups. Three patients developed respiratory depression, and all three were in the bolus plus infusion groups. Two patients failed to complete the study and one disliked PCA. Analysis of pain scores of the remaining 25 patients showed no significant differences between groups. The blood concentrations of alfentanil were slightly higher in the bolus plus infusion groups, but this was not significant. The total amount of alfentanil received was, however, significantly greater in the PCA plus infusion groups (analysis of variance $P < 0.001$).

Good analgesia can be obtained in most patients using any of the above regimens. Success can be improved by adding a background infusion, but this detracts from the inherent safety of PCA and results in an increased rate of respiratory depression.

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EFFECT OF IBUPROFEN ON PAIN DURING INJECTION OF PROPOFOL

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Injection of propofol into peripheral veins produces pain in many patients. Previous work has shown that the addition of lignocaine to the emulsion reduces this pain. The mechanism of pain production is unclear, as propofol does not appear to cause tissue damage. To test the hypothesis that pain production may involve the release of prostaglandins, the effect of a prostaglandin inhibiting non-steroidal anti-inflammatory drug was investigated.

Following Ethics Committee approval, 58 ASA grade I or II female patients were allocated randomly to one of three groups in a double-blind controlled trial. All patients gave written informed consent. Patients in groups 1 and 2 received ibuprofen 400 mg orally 2 h before surgery and group 3 patients received a physically identical placebo. In all groups anaesthesia was induced with propofol injected into a vein on the dorsum of the hand at a constant rate. Patients in groups 2 and 3 were given lignocaine 10 mg added to propofol 20 ml immediately before injection; patients in group 1 received an equal volume of saline. The use of a control group who would receive unmodified propofol was considered to be unnecessary. After half the estimated induction dose had been injected, the patient was asked if the arm was comfortable and the response was assessed on a four-point scale: 0 no pain, 1 sensation, 2 discomfort, 3 pain. The same investigator assessed all 58 patients.

The data were analysed for incidence of pain by comparing pain (3) with the other responses (0–2) as a group (table V). Chi-square was 6.572, $P = 0.0374$. It was, therefore, thought necessary to terminate the trial at this stage.

The study demonstrates that the use of a single dose of ibuprofen is significantly less effective than 0.05% lignocaine in reducing pain on injection of propofol. Although a single dose of ibuprofen 400 mg probably does not maximally

TABLE V. *Pain response of patients*

	Pain response				
Group	0	1	2	3	Total
1	7	2	3	6	18
2	13	4	3	1	21
3	11	4	2	2	19
Total	31	10	8	9	58

block prostaglandin production, the hypothesis that prostaglandin production is implicated in the production of pain on injection of propofol is not supported by this study.

RELATION OF LUMBAR TISSUE DAMAGE AND BACKACHE AFTER DELIVERY

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Backache during pregnancy and in the postpartum period is common, with a reported incidence of 14–45% [1, 2]. Assessment of pain was not localized to ligaments, joints or nerves in these studies. The purpose of this study was to determine the acute traumatic effects of labour and delivery on the lumbar spine in the postpartum period using magnetic resonance imaging.

Postpartum mothers gave written informed consent. Magnetic resonance imaging was performed 24–27 h after delivery on an 0.15 Tesla machine. T_1 weighted spin echo and short inversion time inversion recovery images were obtained in sagittal and parasagittal planes. Clinical assessment of bruising, swelling and tenderness in the lumbar region, the site and severity of pain, its character and spinal movement was made. The position of abnormal tissue fluid accumulation was noted in the magnetic resonance imaging scan and its severity graded.

Seven primiparous and five multiparous women completed the study. Extradural analgesia was required by six patients. Seven women had normal deliveries, two had forcep deliveries and two had Caesarean sections. The most striking feature of the magnetic resonance imaging scan was in the short inversion time inversion recovery sequence which showed high signal, likely to represent oedema in the subcutaneous tissues in all women, extending for a variable number of segments in the lower lumbar region. After Caesarean section two women showed mild changes. Three women had severe changes, one with back pain and limited movement, one with limited movement but no back pain and one with no abnormal clinical findings. The remaining five patients showed moderate changes and one had back pain. Almost all the changes were midline rather than in a lateral position. There were no abnormal findings in the ligaments, muscles or extradural space to account for back pain. In this group of 11 women, two had previously undiagnosed decreased height in one of the discs. Two patients returned for a scan more than 6 weeks after delivery.

The preliminary results of this study suggest that tissue damage following labour and delivery occurs in the dorsolumbar region but it is superficial rather than in the muscles or ligaments. It does not appear to be related to the occurrence of back pain and its severity does not appear to be influenced by lying supine in the postpartum period.

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COMPARISON OF CONTEMPORANEOUS AND RETROSPECTIVE ASSESSMENT OF POSTOPERATIVE PAIN USING VISUAL ANALOGUE SCALE

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The visual analogue scale (VAS) is used widely in clinical research to quantify postoperative pain. The accuracy and reproducibility of VAS have been studied [1] with measurements repeated after a 5-min interval. Some investigators have used a single retrospective VAS 24 or 48 h after surgery [2]. However, retrospective assessment in this manner has not been validated. We have compared assessment of pain using a single retrospective VAS score on the second postoperative day, with repeated contemporaneous VAS scores on the first postoperative day.

We assessed the postoperative pain of 50 patients (ASA I or II) undergoing abdominal hysterectomy. All patients received general anaesthesia. Intermittent i.m. injections of papaveretum were administered on demand after operation. Pain was assessed using a 10 cm VAS every 2 h on the day after operation from 09:00 to 21:00. At 09:00 on the second day after operation, a VAS was used to assess the current experience of pain, and the patients were asked also to record on a separate VAS their overall estimate of pain in the preceding 24 h.

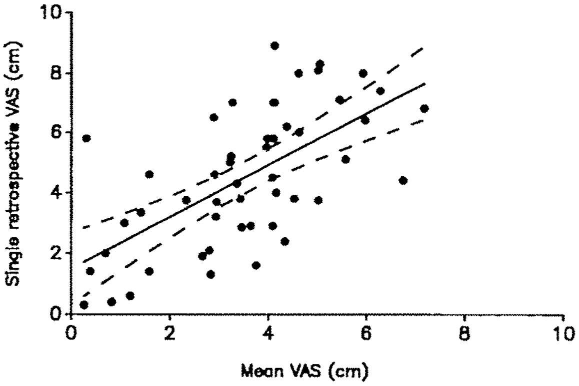

FIG. 2. Relationship between mean contemporaneous and retrospective VAS. Dotted lines indicate 95% confidence intervals of the regression line.

The correlation coefficients between the single retrospective VAS and the mean, median and greatest contemporaneous VAS were statistically significant ($r = 0.63$, 0.63 and 0.66, respectively, all $P < 0.0001$). However, there was a wide scatter of results (fig. 2). There was a less significant relationship between the contemporaneous assessment of pain on day 2 and the retrospective score (made at the same time) of pain over the previous 24-h period.

We conclude that, although there is a statistical relationship between contemporaneous and retrospective assessment of pain using VAS, there is considerable variability between the two methods in individual patients.

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COMPETITIVE ANTAGONISM OF ACETYCHOLINE RECEPTOR INCREASES RECEPTOR NUMBER AND TOLERANCE TO TUBOCURARINE

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We tested the hypothesis that chronic, competitive antagonism of nicotinic acetylcholine receptors (nAChR), even in the absence of immobilization or paralysis, induces proliferation of the receptor and tolerance to the effects of the competitive antagonist. Chronic subparalytic (subliminal) antagonism of nAChR was achieved in rats by an infusion of tubocurarine, at a rate of 0.012 mg kg^{-1} h^{-1} via Alzet mini osmotic pumps inserted under anaesthesia in the subscapular region. The control animals received saline via the pumps. After 2 weeks of tubocurarine or saline, the animals were re-anaesthetized and steady state plasma concentrations of tubocurarine were measured for twitch suppression of gastrocnemius to 75% of control twitch height (CP_{75}). The gastrocnemius and hemidiaphragm AChR were quantitated by ^{125}I-α-bungarotoxin.

No differences in weight gain or mobility were observed between the two groups. The osmotic pump infusion of tubocurarine in the experimental group resulted in a baseline plasma concentration (mean (SEM)) of 0.41 (0.07) μg ml^{-1} on the day of the twitch studies. These concentrations of tubocurarine when achieved acutely would cause a depression of the twitch tension to 60% of control twitch height. The experimental group, however, was able to develop a baseline tension of 50 *g* similar to that of controls. The plasma concentration of tubocurarine required for steady state inhibition was significantly greater in the experimental group as was the number of extrajunctional AChR (table VI). The diaphragmatic nAChR were unchanged between groups.

The study confirms the hypothesis that the chronic presence of tubocurarine induces an up-regulation of nAChR and resistance to tubocurarine even in the absence of immobilization or paralysis. The absence of AChR changes in the diaphragm may be attributable to the higher margin of safety of the diaphragm for neuromuscular blocking drugs compared with peripheral muscles. Chronic administration of tubocurarine-like drugs, as seen in the intensive care unit, may result in tolerance to its effects. Conversely, hyperkalaemia and cardiac arrest associated with the use of suxamethonium in intensive care units may be related to the spread of extrajunctional nAChR induced by chronic use of competitive antagonists of the neuromuscular junction.

TABLE VI. *Changes in nicotine acetylcholine receptors (nAChR) and twitch inhibition to 75% of control twitch height (CP_{75}) in the tubocurarine and control groups (mean (SEM). *$P < 0.05$ compared with control*

	Tubocurarine	Control
Gastrocnemius nAChR (fmol/mg protein)	19.7 (1.8)*	13.4 (1.8)
Diaphragm nAChR (fmol/mg protein)	7.1 (0.5)	7.1 (0.5)
CP_{75} of tubocurarine (μg ml^{-1})	0.8 (0.1)*	0.5 (0.2)

EFFECT OF OXPENTIFYLLINE ON ENDOTOXIN/SMOKE-INDUCED LUNG INJURY

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There is strong evidence that the inflammatory response to sepsis may itself be responsible for many of its complications such as septic shock, multisystem organ failure and the adult respiratory distress syndrome. Oxpentifylline a methylxanthine derivative, suppresses important features of the inflammatory responses to infection and its possible role in attenuating this autodestructive element of severe sepsis has recently aroused considerable interest [1].

Acute lung injury, an important feature of many animal models of sepsis, can be measured by recording the clearance of aerosolized ^{99m}Tc-DTPA from the lung. This clearance reflects the permeability of the alveolar–capillary barrier. We examined the effect of oxpentifylline on a model of endotoxin/smoke-induced lung injury using this technique.

Following sedation and an i.v. bolus of endotoxin 3 μg kg^{-1} (*E. coli* 026:B6, Sigma), New Zealand white, specific pathogen-free rabbits were anaesthetized and tracheotomy performed. Four hours after endotoxin administration, the animals' lungs were ventilated with 20, 20-ml breaths of smoke. Clearance curves for ^{99m}Tc-DTPA were measured before and after smoke. The treatment group ($n = 5$) received oxpentifylline 20 mg kg^{-1} 30 min before the endotoxin, followed by a continuous infusion of 6 mg kg^{-1} h^{-1}. The control animals ($n = 8$) received an equivalent volume of saline.

The half-times for clearance from the lungs are given in table VII. Clearance following endotoxin and smoke was significantly slower in the oxpentifylline-treated group when compared with the controls. (Confidence interval analysis was

TABLE VII. *Effect of oxpentifylline on clearance half times of aerosolized ^{99m}Tc-DTPA from the lungs (min (SEM)). *P = 0.016*

	Control	Oxpentifylline	95% CI ratio
Endotoxin alone	145 (17)	205 (62)	0.7–2.2
Endotoxin + smoke	48 (7.1)	175 (82)*	1.3–6.1

performed on log transformed data so that the 95% confidence intervals (CI) are quoted as a ratio of the sample means.)

The study provides further evidence for the role of oxpentifylline in attenuating the pulmonary effects of endotoxaemia.

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TESTS ON AIRWAY ADJUNCTS USED FOR EXPIRED AIR RESUSCITATION

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Various airway adjuncts are used during expired air resuscitation. These include face shields, mask–valve devices and resuscitation airways. They provide rescuer protection by either non-return valves or filters. Several workers [1, 2] have assessed the effectiveness of these devices in clinical situations but to our knowledge no design specifications have been published nor has any evaluation of their physical characteristics been undertaken.

We measured the resistances of 12 devices with a water manometer at oxygen flows from 5 litre min^{-1} to 30 litre min^{-1} in 5-litre min^{-1} increments. Both rescuer-to-patient (insp) and patient-to-air (exp) resistances were measured. Each test was performed six times. Where possible, several samples of each device were assessed. All resistance measurements (cm H_2O) were made over the full range of gas flows, although only those at 30 litre min^{-1} are shown. No attempt was made to assess the ease of application or clinical efficiency of these devices.

The ability of the valves to prevent expired air from the patient reaching the rescuer ("reflux") was also assessed by noting if there was any increase in resistance when the rescuer port was occluded. The effectiveness of the two filter devices to protect the rescuer was assessed by applying artificial saliva 2 ml (Hypromellose Solution BNF) to the rescuer side and measuring the subsequent increases in resistance to flow and noting any transmission of the medium across the filter. A Pall Biomedical Ultipor bacterial filter was also tested (table VIII).

TABLE VIII. *Inspiratory (Insp.) and expiratory (Exp.) resistances (resist.) of a variety of airway adjuncts for expired air resuscitation. [a] Dual-Aid. Wide variability in samples. Reflux occurs during expiratory flows < 12 litre min^{-1}. [b] MTM Resuscitator. Flap valve has serious leaks at low inspiratory and high expiratory flows. Occlusion of rescuer port at expiratory flows greater than 20 litre min^{-1} results in patient pressure greater than 35 cm H_2O. [c] Resusci face shield. Initial pressures high until the material is saturated. Thereafter the filter is an ineffective barrier to fluid transfer. [d] Hilt-way. At high expiratory flows the filter buckles, producing high resistance. When fluid is applied the hydrophobic nature of the material leads to high resistance*

Model	n	Insp. resist. (cm H_2O)		Exp. resist. (cm H_2O)	Reflux
Valves					
Resusciade (Portex)	5	25		N/A	No
Rondaid (Selles)	1	16		N/A	No
Microshield (Bioglan)	1	5		N/A	No
Life Aid (J & J)	2	0		N/A	No
Lifeway (Weinmann)	1	2		1	No
Mask–valve (Laerdal)	3	3		7	No
Dual-Aid (Vitalograph)	4	5		23–35+	Yes[a]
MTM (Health Products)	2	1		1–35++	Yes[b]
Brook (GH Wood)	4	14		9	No
Sussex (Tandisdale)	1	2		2	No
		Insp. resist.		Exp. resist.	
		Dry	Wet	Dry	
Filters					
Laerdal face shield	4	2	6[c]	2	Fluid leak
Hilt-way (Medifield)	6	8	25	32[d]	Fluid obstruction
Ultipor Filter (Pall)	2	0	1	3	

Recommended criteria for all devices should include rescuer and patient resistances (wet or dry) below 5 cm H_2O at 30 litre min^{-1}. Valves must seat reliably at all flows to prevent reflux and filters must be effective in preventing fluid transfer.

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COMPARISON OF SEDATION WITH MIDAZOLAM OR DIAZEMULS FOR UPPER GASTROINTESTINAL ENDOSCOPY

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Upper gastrointestinal endoscopy under sedation is associated with a significant decrease in arterial oxygen saturation [1]. However, to date no data exist comparing the two most commonly used agents, midazolam and diazemuls. This prospective randomized study was designed to compare the effects of these drugs on arterial pressure and oxygen saturation in 81 patients presenting for routine day-case upper gastrointestinal endoscopy. Patients were allocated randomly to receive midazolam 0.07 mg kg^{-1} or diazemuls 0 21 mg kg^{-1} (midazolam 43, diazemuls 38) [2]. Patients aged 70 yr or more were given half of the calculated dose. Oxygen saturation was measured by an Ohmeda Biox 3700 pulse oximeter applied to the thumb of the right hand and arterial pressure was measured using the Ohmeda Finapres non-invasive continuous arterial pressure measuring device. Systolic, diastolic, mean arterial pressures, heart rate and oxygen saturation were logged from the monitors every 2 s by an Apple Macintosh SE microcomputer.

The monitors were applied after the patient had been positioned in the left lateral position on the trolley. Data were obtained for 2 min before sedation to provide baseline information. The sedative drug was then administered by one of the authors (IF) out of sight of the endoscopist (JH) and the cannula flushed with saline. Data were obtained for 3 min, at which time the endoscopy was started. At the end of the examination, data monitoring continued for a further 2 min at which time the sensors were removed and the patient taken to the recovery area. The endoscopist scored the quality of the sedation on a five-point scale (5 = excellent, 1 = terrible) and also the "ease of endoscopy" (5 = very easy, 1 = extremely difficult).

Mean arterial pressure, oxygen saturation and rate–pressure product data were analysed for the two groups. In each case the data for the pre-sedation period were averaged and the mean used as a baseline. All data for the post-sedation, endoscopy and recovery periods were expressed as changes from these baseline figures. Data for each time point from each patient in the group was then averaged to give a composite set of data for the relevant parameter for the group. Data were analysed separately for the sedation, endoscopy and recovery periods. Because of the variable duration of the endoscopies, only the first 4 min of this information was analysed. Arterial pressure and rate–pressure product data were analysed using ANOVA, the Spearman rank correlation was used to investigate the relationship of oxygen saturation and rate–pressure product and the sedation scores compared using the chi-square test, which was also used for assessment of oxygen saturation changes.

The patient groups were not statistically different in terms of sex, body weight or age. The results of cardiovascular and oxygen saturation changes are shown in table IX.

Comparison of sedation scores showed that diazemuls 0.21 mg kg^{-1} produced greater sedation than midazolam 0.07 mg kg^{-1} ($P < 0.05$). There was a significant negative correlation between rate–pressure product and oxygen saturation for both drugs during endoscopy ($P < 0.01$).

TABLE IX. *Changes in arterial pressure (AP), rate–pressure product (RPP) and oxygen saturation Sa_{O_2} following administration of midazolam (M) and diazemuls (D)*

	Mean AP	RPP	Sa_{O_2}
Sedation	ns	D < M $P < 0.001$	ns
Endoscopy	ns	D < M $P < 0.0004$	M < D $P < 0.001$
Recovery	D < M $P < 0.002$	D < M $P < 0.0001$	ns

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GASTRIC EMPTYING IN PREGNANCY

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Delay in gastric emptying during pregnancy resulting in increased residual volume may increase the risk of aspiration of gastric contents during anaesthesia. Its presence may also influence the absorption of orally administered drugs, such as H_2 antagonists, administered in the preoperative period. At present, the evidence for delay in gastric emptying in pregnancy is inconclusive [1, 2]. In this study the rate of paracetamol absorption was used to measure gastric emptying [3] in each of the three trimesters of pregnancy and in a non-pregnant control group.

Following Ethics Committee approval and informed consent, four groups of 15 patients were studied. All patients were fit, of childbearing age, presenting before operation and fasted for a minimum of 6 h. The four groups were: group A, non-pregnant women presenting for minor gynaecological surgery (control); group B, women in the first trimester before suction termination of pregnancy (TOP); group C, women in the second trimester before extra-

TABLE X. *Pharmacokinetic parameters of paracetamol in the four groups studied. Mean (±SEM)*

	Cmax (μg ml^{-1})	tmax (min)	AUC$_{60}$ (μg min ml^{-1})	AUC$_{120}$ (μg min ml^{-1})
Control	28.19	61	850.65	2153
	(1.62)	(6.85)	(77.82)	(111.94)
TOP	23.01	74	529.62	1502.4
	(2.18)	(8.54)	(89.59)	(128.75)
PG	36.7	59	833.92	1784.67
	(2.54)	(9.32)	(152.63)	(211.72)
Sect	28.10	45	979.83	2069.98
	(2.12)	(4.89)	(96.21)	(123.87)

amniotic prostaglandin termination of pregnancy (PG); group D, women at term before elective Caesarean section (Sect). An oral dose of paracetamol 1.5 g was given with 50 ml of water and venous blood samples were withdrawn at 15-min intervals for 120 min. Plasma paracetamol concentrations were measured by high pressure liquid chromatography. Data were analysed using one-way analysis of variance.

There was no significant difference in the mean maximum plasma paracetamol concentrations (Cmax) or the time to mean maximum paracetamol concentrations (tmax) between the groups ($P > 0.05$). There was a statistical difference in the area under the curve at 60 min (AUC$_{60}$) ($P < 0.05$) between the control and TOP groups, which was evident at 120 min (AUC$_{120}$) ($P < 0.017$) (table X).

In conclusion, no significant delay in gastric emptying was demonstrated in any of the three trimesters of pregnancy in this study.

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COMPARISON OF THE EFFECTS OF ORAL NIZATIDINE AND RANITIDINE ON GASTRIC VOLUME AND pH

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Aspiration of gastric contents remains a major cause of anaesthetic mortality, particularly in the obstetric patient [1]. First described in 1946 by Mendelson, the severity of the syndrome depends on the acidity and volume of the gastric contents. Alkalis and H$_2$ receptor blocking drugs have been used to reduce the acidity of the gastric contents before induction of anaesthesia.

Nizatidine is an H$_2$ receptor blocking drug which is equipotent to rantidine, and six times more potent than cimetidine. It has a high oral bioavailability (90%) and reaches peak plasma concentrations within 2 h of oral administration [2]. We compared the effects of oral nizatidine and ranitidine on gastric pH and volume in day surgical patients undergoing laparoscopy.

Ninety patients were allocated randomly to three groups of 30 each, receiving nizatidine 150 mg, ranitidine 150 mg or placebo orally at least 45 min before induction of anaesthesia. After tracheal intubation, gastric contents were aspirated using a 14-French gauge red rubber orogastric tube. Venous blood samples were taken at the same time. Samples were repeated every 15 min and at the end of the procedure. The volumes and pH of the gastric aspirates were measured. Blood samples were centrifuged and plasma stored at −20 °C before drug analysis.

There were no differences between the aspirated gastric volumes of the three groups. This was the case when patients both with and without a measurable gastric aspirate were considered. Two patients in the nizatidine group in whom no gastric aspirate could be obtained had plasma concentrations of drug less than the therapeutic range (> 600 ng ml^{-1}), while all patients in the ranitidine group without gastric aspirate had plasma concentrations of drug greater than the therapeutic range (> 100 ng ml^{-1}).

The median pH values in the treated groups were greater than in the placebo group ($P < 0.001$). There were no differences between the nizatidine and ranitidine groups. If the number of patients at risk of Mendelson's syndrome are calculated in terms of both pH < 2.5 and volume > 25 ml, there were none in the nizatidine group, three in the ranitidine group, and two in the placebo group (not significant); when pH < 2.5 was taken as the only risk factor, there were two patients in the nizatidine group, six in the ranitidine group (not significant) and 19 in the placebo group ($P < 0.001$).

If data were divided arbitrarily into time intervals of 45–90 min and > 90 min between test drug administration and induction of anaesthesia, all patients in the nizatidine and ranitidine groups with gastric pH < 2.5 received the drugs in the 45–90 min interval. Hence, more patients in the ranitidine group were at risk, suggesting that a latent period of more than 90 min is required before ranitidine increases pH safely.

This study shows that nizatidine is as effective as ranitidine in increasing gastric pH, but when a quicker onset of action is desired, nizatidine may be the better agent.

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SIMULTANEOUS INTRAOPERATIVE OESOPHAGEAL AND TRACHEAL pH MONITORING

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Regurgitation and subsequent aspiration of gastric contents remains a major cause of morbidity and mortality for patients under anaesthesia. The occurrence of regurgitation has been estimated at 14–26 % during a variety of anaesthetic techniques [1, 2]. Aspiration around tracheal cuffs in patients undergoing general anaesthesia is also reported widely [3].

Using modern fine antimony pH probes, we have studied oesophageal and tracheal pH simultaneously during the perioperative period to determine accurately the incidence of regurgitation and aspiration in patients undergoing general anaesthesia.

Informed consent, as described in the Declaration of Helsinki, was obtained from 36 patients scheduled for elective surgery under general anaesthesia with tracheal intubation. Patients were aged between 18 and 80 yr. Exclusion criteria included patients with a history of peptic ulcer disease, oesophageal reflux, a recent history of ingestion of antacids or H_2 blockers, pregnancy and those having or having had upper gastrointestinal surgery.

Oesophageal and tracheal pH were monitored using a Synectics system comprising two indwelling antimony tipped probes (oesophageal and tracheal) connected to two portable Digitappers. The Digitappers stored the data for analysis with Synectics Oesophagram 2.1 on an IBM PC. During periods of recording, pH was displayed continuously for reference. A regurgitation or aspiration event was defined as a decrease in pH to 4.0 or less.

In the induction room, the oesophageal probe was passed nasally into the stomach and then withdrawn leaving the tip 25 cm from the nose in the upper oesophagus. Before induction the tracheal probe was passed down the tracheal tube through the Murphy eye beyond the cuff to project no further than 2 cm. A standard procedure for anaesthesia was then instituted, using i.v. induction and maintenance with inhalation agents. The tracheal probe was removed at extubation and the oesophageal probe removed before discharging the patient from the recovery room.

Nine patients (25 %) regurgitated in the perioperative period. On no occasion did aspiration occur beyond the cuffed tracheal tube (table XI).

There is a high risk of oesophageal regurgitation in the perioperative period (25 %). A significant number of patients (16.7 %) continue to regurgitate during recovery from general anaesthesia. The regurgitation is usually clinically undetectable.

TABLE XI. *Regurgitation episodes during the preoperative (Pre-op.), intraoperative (Intra-op.) and postoperative (Post-op.) periods*

	Pre-op.	Intra-op.	Post-op.
Patients	3 (8.3 %)	7 (19 4 %)	6 (16.7 %)
pH range	1.8–3.8	1.0–3.8	0.9–3.9

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PRELIMINARY OBSERVATIONS OF VOCAL CORD MOVEMENTS ON INDUCTION OF ANAESTHESIA WITH PROPOFOL OR THIOPENTONE

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Previous work has suggested that following induction of anaesthesia with propofol the vocal cords are in an abducted position [1, 2]. Other studies have commented that oral airways are tolerated well following induction with propofol [3]. The object of this study was to record on videotape the movements of the vocal cords on induction of anaesthesia with either propofol or thiopentone.

Six patients aged 34–78 yr undergoing general surgery were allocated randomly to receive either propofol or thiopentone. All patients had normal laryngeal function and all were premedicated with oral benzodiazepines 1 h before operation. Patients were given a benzocaine lozenge on leaving the ward and on their arrival in the anaesthetic room, monitoring was commenced using an ECG monitor and pulse oximeter. Lignocaine paste (5 %) was applied to the nasal mucosa, and after 10 min a size 6 nasopharyngeal airway was inserted. A 16-gauge cannula was inserted into a forearm vein. Preoxygenation was undertaken for 5 min with 100 % oxygen via a specially adapted close-fitting face mask. An Olympus LF1 fibrescope with a video camera attached to the eyepiece was introduced through the mask and passed down the nasopharyngeal airway until a clear view of the larynx was obtained. The recordings were made on a Sony 5 Series U-Matic tape recorder with sound recorded to note events. When clear and steady pictures of the larynx were obtained, anaesthesia was induced using thiopentone 5 mg kg^{-1} or propofol 2 mg kg^{-1} i.v. injected over 30 s.

The start of the injection and the loss of eyelash reflex were recorded on sound track. Video recording continued for 2 min after the start of the injection.

The tapes were played back on video equipment with a freeze-frame facility and measurements made of the angle between the vocal cords using a goniometer. Measurements were made in the awake state and every 5 s following induction of anaesthesia for 2 min.

The results indicate that there may be a difference in the movements of the vocal cords following induction of anaesthesia with thiopentone or propofol. Following thiopentone the vocal cords adduct and the larynx may close completely for 20–30 s, whereas following propofol the vocal cords remain abducted and the larynx remains open. A score of 2, 1 or 0 was given if the angle between the vocal cords was $>30°$, $<30°$ or closed, respectively (fig. 3).

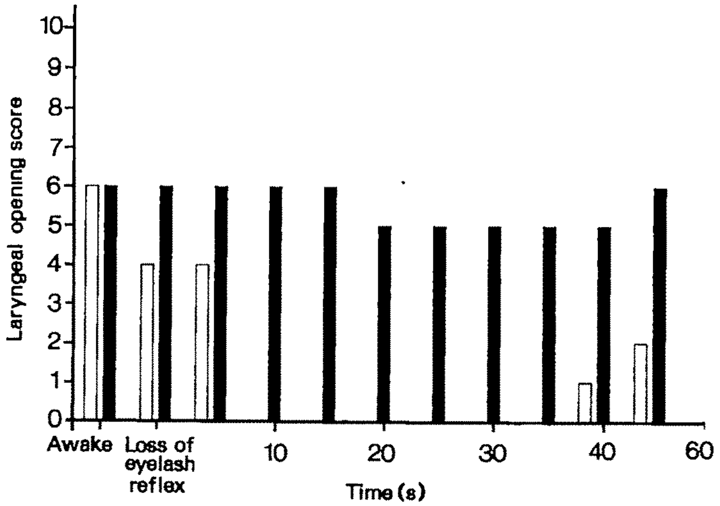

FIG. 3. Laryngeal opening score following induction of anaesthesia with thiopentone or propofol.

ACKNOWLEDGEMENT

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TOWARDS A SINGLE INDEX FOR QUANTIFYING OSSEOUS FACTORS IN DIFFICULT LARYNGOSCOPY

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X-ray layngoscopy study of difficult intubation patients has shown a single angle, "EoI" to be an indicator for degree of difficulty. EoI varies with head and neck posture, and has a maximum value near the "standard intubating position" [1]. A distance less than 6 cm from the lower border of the mandible to the thyroid notch (when the head is extended fully) is also said to predict difficulty in adults [2]. A recently derived index could supersede both.

Figure 4 shows five x-ray points: I, tip of upper incisors; T, anterior airway above cords; S, midpoint (lower border of mandible to incisor tip) of inside of jaw; J, condylar midpoint; and X, intersection of lines IT and JS. β is the angle SXT. The new index is defined as:

$$\frac{XS}{JS} \times \frac{XT}{IT} \times \operatorname{Sin} \beta$$

The index was assessed using x-ray laryngoscopy films from earlier studies, including 10 normal volunteers, eight difficult laryngoscopy patients and eight with a history of difficult laryngoscopy during pregnancy [3]. Seven different laryngoscopy grades were observed. Spearman Rank correlation (r) for EoI alone, was 0.832 ($P < 0.001$). XS/JS and Sin β individually had r values of 0.789 and 0.756, respectively (both $P < 0.001$), but XT/IT was not correlated ($r = 0.265$, $P > 0.5$). With the combination (Sin β) × XS/JS, r was 0.795 (i.e. still less than EoI alone) but 0.856 for the new index.

The new index is suggested to be superior to its predecessors in describing osseous factors causing difficult laryngoscopy. The relevance of the angle β has not been reported previously. In volunteers in the standard position, the mean

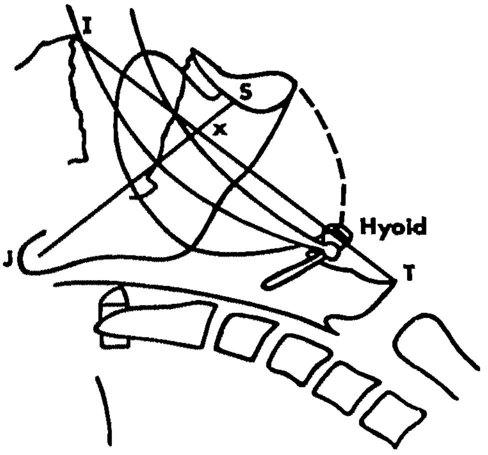

FIG. 4. A normal x-ray laryngoscopy. The blade tip is behind the body of the hyoid and the epiglottis is also pulled forward. The dotted line shows the anterior limit of the tongue muscle bulk. (See text for explanation of reference points.)

for β was 81.5° (SD 5.4). Values less than 70° were found in two difficult laryngoscopy patients. It appears that this factor alone could cause difficulty. The results also imply that optimal laryngeal exposure requires that the mouth does not remain open widely after insertion of the laryngoscope blade.

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AORTIC CROSS CLAMP DURATION AND HAEMODYNAMIC PERFORMANCE IN AN EXPERIMENTAL NORMOVOLAEMIC AND HYPOVOLAEMIC MODEL

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Haemodynamic changes following cross clamping are influenced by preoperative coronary circulation and myocardial function, the site of cross clamp application, the intravascular volume, the anaesthetic agents and techniques used and the surgical pathology [1]. The effects of aortic cross clamp duration are uncertain, but recent data suggest that a cross clamp time of more than 70 min is associated with increased cardiac morbidity [2]. This study was undertaken to evaluate the influence of infrarenal aortic cross clamp duration on haemodynamic performance in normovolaemic and hypovolaemic dogs.

Mongrel dogs (weight 19 (SD 1 8) kg were assigned randomly to two treatment groups: group 1, normovolaemic group; group 2, hypovolaemic group. Blood was withdrawn via the femoral arterial line to reduce pulmonary capillary wedge pressure to 3 mm Hg (15–30% estimated blood volume). Intravascular volume deficit was replaced with whole blood and administration of crystalloid after 45 min. Anaesthesia was induced with thiopentone 20 mg kg^{-1} and maintained with 0.5–1.5% halothane in oxygen. The femoral and common carotid arteries were cannulated and a triple lumen pulmonary catheter was placed for triplicate thermodilution cardiac output monitoring. Measured and derived haemodynamic data, including cardiac index (CI), left ventricular stroke work index (LVSWI) and systemic vascular resistance (SVR) were obtained at defined intervals. The duration of cross clamp was either 60 or 120 min in both groups. Data were expressed as mean (SEM). Statistical analysis included Wilcoxon two-sample rank sum test. $P < 0.05$ was considered significant.

Control values (preclamp for CI, LVSWI and SVR) were similar in both groups. Prolonged cross clamping was associated with a decrease in CI and LVSWI in both groups. SVR increased in group 2 after 120 min cross clamping (fig. 5). SVR decreased in both groups after declamping. Acid–base studies revealed a progressive metabolic acidosis in all groups.

This study suggests that prolonged cross clamping has deleterious effects on haemodynamic performance. Possible mechanisms include increased metabolic and acid–base disturbances. Further studies evaluating technical improvements aimed at reducing cross clamp duration and pharmacological intervention to counteract adverse metabolic influences are indicated.

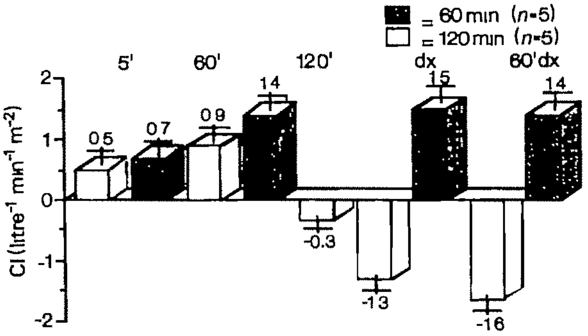

FIG. 5. Changes in cardiac index (CI) after 60 min and 120 min cross clamping in the hypovolaemic group.

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ADRENOCEPTOR AND NEUROENDOCRINE RESPONSES TO AORTIC CROSS CLAMP AND RELEASE DURING ABDOMINAL AORTIC SURGERY

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The neuroendocrine responses to surgical stress are characterized by increases in plasma concentrations of catecholamines, cortisol, antidiuretic hormone (ADH) and human growth hormone [1]. Abdominal aortic surgery involves the application and release of aortic cross clamps and is associated with significant changes in cardiovascular performance [2]. The objectives of this study were to quantify the humoral and beta-adrenoceptor changes following aortic cross clamping and to correlate these changes with haemodynamic performance.

Fourteen patients presenting for elective abdominal aortic surgery were studied prospectively. Preoperative cardiac status was assessed by physical examination, electrocardiogram and resting left ventricular ejection fraction determination. Patients taking beta-receptor agonists/antagonists and those with signs of left ventricular dysfunction were excluded. A standardized anaesthetic technique was used for all patients studied. Radial and pulmonary artery catheters were inserted. Fentanyl 50 $\mu g\ kg^{-1}$ was administered to induce anaesthesia and vecuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. Controlled normocapnic ventilation was commenced with oxygen, 0 25–0.5%

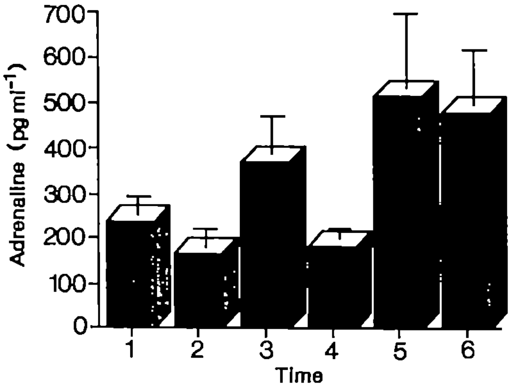

FIG. 6. Changes in the circulating plasma concentrations of adrenaline at: 1, 3 min before induction; 2, 3 min after induction; 3, 3 min before aortic cross clamp; 4, 3 min after aortic cross clamp; 5, 3 min before aortic cross clamp release; 6, 3 min after post-aortic clamp release.

isoflurane and fentanyl infusion 30 μg kg^{-1} h^{-1}. Measured and derived haemodynamic data, including cardiac index (CI), left ventricular stroke work index (LVSWI) and systemic vascular resistance (SVR) were obtained 3 min before and after induction of anaesthesia, aortic cross clamping and release. Plasma adrenaline, noradrenaline, cortisol and lymphocyte beta-adrenoceptor density and distribution were measured at the same time points. Catecholamine concentrations were measured by radioimmunoassay. Beta-adrenoceptor density and distribution between cell surface and cytoplasm were measured by radio-ligand binding. Data were expressed as mean (SEM). Paired Student's *t* test and linear regression analysis were performed. $P < 0.05$ was considered significant.

Abdominal aortic cross clamping was associated with significantly increased SVR and decreased LVSWI and circulating plasma concentrations of adrenaline (fig. 6). A positive correlation between reduced plasma adrenaline and LVSWI and a negative correlation between reduced adrenaline and increased SVR were observed. No significant changes in plasma concentrations of noradrenaline and cortisol were noted following aortic cross clamping. The mean percentage of beta-adrenoceptors residing within the cytoplasm was increased before induction. The percentage of internalized beta-receptors remained unchanged following aortic cross clamping.

The reduced beta-adrenoceptor density and increased cytoplasm distribution observed before surgery suggests that this patient population may have a decreased cardiac responsiveness to beta adrenergic agonists.

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ONSET OF NEUROMUSCULAR BLOCK—AN HYPOTHESIS

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One of the characteristics of non-depolarizing neuromuscular block is its relatively slow onset, which for paralysis of the adductor pollicis muscle in man, for an ED$_{90}$ dose, is 3–4 min. In contrast, the onset time for depolarizing neuromuscular block is rapid (less than 1 min). We propose an hypothesis based on the concept of the margin of safety of neuromuscular transmission to explain this difference in speed of onset.

Following the injection of a neuromuscular blocking agent, a sequence of events occurs before the clinical effect is produced. These can be characterized as: (1) distribution, (2) penetration of the neuromuscular synaptic cleft, (3) passage through the cleft to receptors and (4) reaction with receptors. The physical similarity between molecules of both depolarizing and non-depolarizing neuromuscular blocking agents suggests that it would be difficult to support a theory that explains differences in onset time between these agents by invoking differential delays in phases (1), (2) and (4) above. The delaying effect of the interaction between molecules of neuromuscular blocking agents and the contents of the synaptic cleft (biophase delay—(3)) may serve to limit the rate of increase in concentration of neuromuscular blocking agent molecules at the receptors, but should likewise be the same for the two classes of neuromuscular blocking agents.

In accordance with the concept of the margin of safety, it is assumed that over 80 % of receptors must be occupied by a non-depolarizing drug to produce block of sufficient junctions to give 90 % depression of the twitch response. The corollary of this is that for acetylcholine or depolarizing neuromuscular blocking agents to depolarize motor endplates successfully, only 20 % of receptors need be occupied. Given the supposition that molecules of all neuromuscular blocking agents reach junctional receptors at similar times and rates, we hypothesize that the difference in onset times between depolarizing and non-depolarizing neuromuscular blocking agents is explained by the different proportion of junctional receptors that need to be occupied in order to gain clinical effect.

We offer the following supporting evidence based on laboratory and human studies performed: (a) after α-bungarotoxin was administered to a rat phrenic nerve preparation until 90 % block was achieved, it was still possible to observe a blocking effect when suxamethonium was administered; (b) the occupation of a significant proportion of receptors with a small dose of non-depolarizing neuromuscular blocking agent shortens onset time when a larger dose is then given (the priming principle). This has been confirmed with the use of α-bungarotoxin as the "priming" agent in the rat phrenic nerve preparation; (c) the onset time of vecuronium is substantially shorter in myasthenic patients than in those with normal neuromuscular function; (d) when clinical doses of vecuronium and suxamethonium are given to humans simultaneously, the onset of action is delayed and fade in the train-of-four is seen.

TABLE XII. *Plasma and urinary clearance of atracurium, laudanosine and MQA. Mean (SEM)*

	Mean plasma clearance (ml kg^{-1} min^{-1})	Mean urinary clearance (ml kg^{-1} min^{-1})
Atracurium	7.2 (0.5)	0.6 (0.2)
Laudanosine	3.9 (0.6)	0.3 (0.1)
MQA	6.1 (0.6)	0 6 (0.2)

URINARY CLEARANCE OF ATRACURIUM, LAUDANOSINE AND MONOQUATERNARY ALCOHOL IN THE INTENSIVE CARE PATIENT WITH NORMAL RENAL FUNCTION

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Atracurium is thought to be excreted unchanged in the urine in only small quantities. However, the exact amount has not been defined in humans. Indirect evidence has suggested that a significant amount of atracurium undergoes organ clearance [1, 2]. Because of the difficulties of measuring urinary excretion of drugs during general anaesthesia, it was decided to study the urinary clearance of atracurium and its metabolites, laudanosine and monoquaternary alcohol (MQA), in patients receiving the drug by constant infusion in the intensive therapy unit. Urinary clearance rates were compared with the steady state plasma clearance of these substances.

Plasma and urinary concentrations of atracurium, laudanosine and MQA were measured in seven patients with normal renal function (mean (SEM) creatinine clearance 78.3 (11.4) ml min^{-1}: 1.01 (0.12) ml kg^{-1} min^{-1}) using an HPLC technique described previously [3]. All patients were receiving constant infusions of atracurium 0.3–0.8 mg kg^{-1} h^{-1}, morphine 2–10 mg h^{-1} and midazolam 2–10 mg h^{-1} together with dopamine 2–5 μg kg^{-1} min^{-1}. Written consent for the study was obtained from the next-of-kin. The plasma samples (4 ml) were collected from a radial arterial line and the urine samples (5 ml) were collected at the same time from the connection of the urinary catheter with the urine collecting bag. A total of 66 paired samples was collected from the seven patients when they were known to have reached steady state plasma concentrations of atracurium and its metabolites. The steady state plasma clearance was derived from the infusion rate (ng kg^{-1} min^{-1})/plasma concentration (ng ml^{-1}) and the urinary clearance from the formula UV/P, where U is the urinary concentration in ng ml^{-1}, V the urinary flow rate in ml min^{-1} (measured over the preceding 1-h period) and P the plasma concentration in ng ml^{-1}.

The amount of atracurium, laudanosine and MQA excreted through the kidney was approximately 8 %, 9 %, and 10 %, respectively, of that cleared by the plasma (table XII) in the presence of a renal dose of dopamine.

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DOXAPRAM- AND NEOSTIGMINE-EVOKED ANTAGONISM OF VECURONIUM NEUROMUSCULAR BLOCK

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The respiratory stimulant doxapram increases minute ventilation following general anaesthesia without affecting analgesia [1]. Doxapram has also a dual effect in an isolated nerve–muscle preparation; with doxapram alone, muscular contraction is increased and in the presence of tubocurarine, neuromuscular block is enhanced [2]. We decided therefore to study the action of doxapram given at the end of general anaesthesia on the antagonism of neuromuscular block.

Ethics Committee approval was received and informed consent obtained from all patients. Each patient received oral lorazepam as premedication. Anaesthesia was induced with thiopentone and maintained with nitrous oxide, oxygen, 0.5 % halothane and fentanyl 2–5 μg kg^{-1}. Neuromuscular block was achieved with a bolus dose of vecuronium and monitored using a Relaxograph (Datex) modified to produce trains-of-four every 12 s. Electrodes were attached to the hand and wrist to record the evoked compound EMG from the adductor pollicis muscle following ulnar nerve stimulation. Ventilation was controlled to maintain normocapnia. Neuromuscular block was maintained such that the height of the first contraction of the train-of-four (T1) was approximately 10 % of control using additional increments of vecuronium as necessary. At the end of surgery, the action of vecuronium was allowed to decay spontaneously until T1 was 20 % of control. Patients then received randomly either neostigmine 0.5 mg kg^{-1} with glycopyrrolate 0.01 mg kg^{-1} or neostigmine, glycopyrrolate and doxapram 0.5 mg kg^{-1}. When the T1 height had recovered to a maximum, halothane and nitrous oxide were discontinued and the trachea extubated when the patient was awake.

There were 29 patients in the control group and 23 in the doxapram group. The two groups did not differ significantly with respect to mean age, weight, duration of operation or total dose of vecuronium. Mean (SEM) time to recovery of T1 from 25% to 75% of control in the doxapram group was 138(21) s and in the control group 95(13) s. These differences were significant ($P = 0.014$, Mann–Whitney test). Times for the train-of-four ratio to recover from 25% to 75% were also shorter in the control group 221(22) s than in the doxapram group 252(25) s. These differences were not significant.

These results suggest that antagonism of vecuronium neuromuscular block by neostigmine is retarded in the presence of doxapram 0.5 mg kg^{-1}. In view of the known action of doxapram at the neuromuscular junction, this may reflect an interaction at that site.

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COMPARISON OF ONSET TIME AND DURATION OF ACTION OF PIPECURONIUM WITH HIGH DOSE VECURONIUM DURING ISOFLURANE AND PROPOFOL ANAESTHESIA

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We compared the effect of nitrous oxide anaesthesia supplemented with either isoflurane or propofol on onset time, duration of action and cumulation of vecuronium and pipecuronium, using doses which have similar durations of action ("equidurational").

Sixty patients were allocated to four equal groups: group VI received vecuronium 0.15 mg kg^{-1} and isoflurane; group VP received vecuronium 0.2 mg kg^{-1} and propofol; group PI received pipecuronium 0.06 mg kg^{-1} and isoflurane; and group PP received pipecuronium 0.06 mg kg^{-1} and propofol. Neuromuscular block was assessed with a Datex Relaxograph. Onset time was defined as the time between administration of the neuromuscular blocking agent and the time when the first "twitch" (T1) of the train-of-four reached less than 5% of control. Top-up doses of neuromuscular blocking agent (20% of the initial dose) were given when T1 returned to 10% of control. Statistical analysis was performed with unpaired Student's *t* tests. A probability of less than 0.05 was considered significant.

Mean age and weight of the four groups did not differ significantly. Table XIII gives the mean, SD and median onset times and durations of both the initial and first top-up doses of neuromuscular blocking agent for the four groups.

Group PI showed a modest degree of cumulation.

TABLE XIII. *Mean, SD and median onset times and duration of the initial and first top-up doses of neuromuscular blocking agents in the four groups.* $P < 0.05$ *compared with:* * *VI;* † *VP;* ‡ *PI;* § *PP*

Group	Onset time (min)	Duration of initial dose (min)	Duration of first top-up (min)
VI			
Mean	1.57‡§	48.6	27.9
SD	0.50	10.8	10.8
Median	1.50	46.0	28.0
VP			
Mean	1.69‡§	42.6	23.1‡
SD	0.38	8.5	4.7
Median	1.75	42.0	24.0
PI			
Mean	3.28*†§	42.1	31.3†
SD	0.78	12.2	6.6
Median	3.10	44.0	30.0
PP			
Mean	3.97*†‡	48.5	26.9
SD	0.72	25.1	10.3
Median	3.87	37.0	27.0

The potentiating effect of isoflurane may explain the shorter onset times of groups VI and PI when compared with groups VP and PP, and the longer duration of the initial dose and first top-up dose of group VI than group VP. Group PP had a longer mean initial dose duration than group PI; however, the median duration of group PP was shorter than PI. The longer half-life of pipecuronium, combined with the potentiating effect of isoflurane may explain the cumulation seen in group PI.

Our results confirm that vecuronium 0.15–0.2 mg kg^{-1} and pipecuronium 0.06 mg kg^{-1} are suitable for providing 50–60 min of surgical relaxation during isoflurane or propofol anaesthesia. If top-up doses are restricted to 20% of the initial dose, cumulation is minimal. However, the use of large doses of vecuronium in preference to pipecuronium may offer clinical advantage in terms of faster onset time.

STUDY OF BIOCHEMICAL CHANGES FOLLOWING SUXAMETHONIUM ADMINISTRATION IN CHILDREN WITH STRABISMUS

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It has been suggested that children with strabismus may have latent muscle disease and are more susceptible to development of masseter spasm and malignant hyperthermia following suxamethonium administration [1]. As a group they might be expected to show exaggerated biochemical changes with its use, which may be a pointer to more serious sequelae of suxamethonium administration in such children. We investigated this, prospectively in the present study.

One-hundred-and-twenty children between the ages of 3 and 12 yr were included in this study. Half were scheduled to undergo surgery for correction of strabismus and the remainder, undergoing tonsillectomy, were controls. Within each group children were allocated randomly to thiopentone 4–5 mg kg^{-1} (T), halothane (H) or isoflurane (I) with nitrous oxide and oxygen for induction of anaesthesia. Groups T and H received suxamethonium 1 mg kg^{-1}.

Venous blood samples (2 ml) were withdrawn before and at 1, 3 and 5 min after administration of suxamethonium for estimation of serum potassium and total calcium concentrations. Baseline samples and a sample taken 24 h later were analysed for serum creatinine phosphokinase (CPK) concentrations.

Twenty patients were excluded from analysis because of the unsatisfactory condition of the blood samples. The results shown in table XIV are thus based on 100 children. Administration of suxamethonium resulted in a significant increase in serum concentrations of potassium and CPK in group H. The increase in CPK was more modest in group T and minimal in group I. Serum potassium decreased in group T with minimal changes in group I. Serum concentrations of calcium showed a small but significant decrease in all groups receiving suxamethonium.

Our results suggest that biochemical changes following suxamethonium are dependent on the anaesthetic agents used rather than on the presence or absence of strabis-

TABLE XIV. *Mean* (SD) *maximum biochemical changes in the strabismus and control groups after administration of thiopentone* (*T*), *halothane* (*H*) *or isoflurane* (*I*)

	Strabismus			Control		
	T	H	I	T	H	I
n	16	19	17	16	13	19
Calcium	−0.044	−0.051	−0.004	−0.043	−0.028	−0.019
(mmol litre^{-1})	(0.06)	(0.07)	(0.05)	(0.05)	(0.04)	(0.06)
Potassium	−0.35	+0.26	+0.03	−0.13	+0.53	+0.08
(mmol litre^{-1})	(0.38)	(0 40)	(0.49)	(0.33)	(0.33)	(0.42)
CPK	+56	+596	+11	+279	+406	+29
(μmol litre^{-1})	(119)	(956)	(117)	(474)	(661)	(79)

mus. These results support recent work suggesting that children with strabismus do not respond differently to suxamethonium [2, 3].

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I.V. DANTROLENE BEFORE DAY-CASE SUXAMETHONIUM USE: DOMICILIARY ASSESSMENT OF MORBIDITY

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Suxamethonium myalgia may contribute to significant postoperative morbidity following minor operations. We studied dental patients on afternoon day-case lists admitted to a dedicated day-case ward. All were ASA grade I, aged between 18 and 45 yr and gave signed, informed consent to participate in the study.

Patients were allocated randomly to receive placebo or i.v. dantrolene 0.6 mg kg^{-1} 5 min before suxamethonium. All were anaesthetized using propofol, suxamethonium and spontaneous ventilation with nitrous oxide in oxygen and isoflurane supplemented with fentanyl 0.05 mg and droperidol 0.5 mg, by either investigator FDS or ASL. Blood samples were drawn before induction and at up to 40 min after induction. The normal day-case routine was otherwise unchanged.

Patients were visited at home on both the first and second mornings after operation by the third investigator (SOS) between 10:00 and midday. On each visit patients were assessed and scored for a number of subjective indices of morbidity as in our previous presentation [1]. These included myalgia attributable to suxamethonium (scored 0–5), pain from operation site (0–3), and day-time activity (0 = in bed to 3 = normal activity). A further blood sample was drawn on each visit.

We present data on the first 20 patients of each group to complete the study (table XV). On the first day there was considerable morbidity. Total operation site pain was similar between groups but total suxamethonium myalgia ($P < 0.005$, Mann–Whitney) and increase in plasma concentrations of creatinine kinase from before induction ($P < 0.05$, *t* test) were significantly reduced by dantrolene pretreatment compared with the control group. No patient was well enough to return to work. There were no side effects attributable to i.v. dantrolene pretreatment, unlike oral dantrolene [2].

On the second day, total myalgia score in both groups was similar to day 1, although activity had improved significantly. However, only four patients in each group were able to return to work or normal activity.

TABLE XV. *Postoperative data* (*mean* (*range*)) *in the control and dantrolene pretreatment groups*

	Control		Treatment	
	Day 1	Day 2	Day 1	Day 2
No. of patients	20		20	
Suxamethonium pain (Max 100)	31 (0–5)	35 (0–4)	7 (0–3)	7 (0–3)
Operation site pain (Max 60)	27 (1–3)	27 (0–3)	31 (1–3)	30 (1–3)
Activity (Max 60)	25 (0–2)	40 (0–3)	25 (0–2)	35 (0–3)
Mean CK increase (iu)	411 (−9–3941)	239 (−14–2166)	4 (37–157)	−16 (−105–14)

In conclusion, dantrolene pretreatment significantly reduced suxamethonium myalgia without apparent side effects, but had no other impact on overall morbidity following day-case dental surgery.

ACKNOWLEDGEMENT

We wish to thank Norwich Eaton Ltd for financial assistance and Mr W. Collins for undertaking the creatinine kinase assays.

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POSTER PRESENTATIONS

DIAZEPAM PHARMACOKINETICS: COMPARISON OF TWO FORMULATIONS IN THREE PATIENT GROUPS UNDERGOING GENERAL ANAESTHESIA

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A difference in bioavailability between diazepam solubilized in propylene glycol (solution) and soya bean oil (emulsion) has been demonstrated following i.v. injection in adult volunteers [1, 2]. To investigate whether this difference applies to patients undergoing major gynaecological surgery we studied three groups of patients undergoing elective abdominal hysterectomy; control, obese (body mass index >25) and elderly (>65 yr).

Following Ethics Committee approval and written informed consent, 30 ASA I and II patients were studied. In each group, patients were allocated randomly to receive diazepam as either emulsion or solution.

All patients received papaveretum 10 mg and prochlorperazine 12.5 mg i.m. 1 h before operation. Anaesthesia was induced with thiopentone 4 mg kg^{-1}, fentanyl 100 µg and vecuronium 0.1 mg kg^{-1}. The trachea was intubated and anaesthesia was maintained with 66% nitrous oxide and 0.5–1% isoflurane in oxygen. After induction of anaesthesia diazepam 0.2 mg kg^{-1} was given i.v. Blood samples (10 ml) were obtained from the contralateral arm before diazepam injection and at 5, 10, 15, 30 min and 1, 2, 4, 8, 12 and 24 h thereafter. Blood was centrifuged and plasma stored at −20 °C for subsequent analysis for concentrations of diazepam using gas–liquid chromatography.

AUC to infinity, plasma clearance, elimination half-life and volume of distribution were calculated for each patient using the Pharm PCS and Elsfit computer programs.

There was no statistically significant difference in pharmacokinetic values for diazepam emulsion or solution within or between any of the three patient groups (ANOVA, Kruskal–Wallis). When the groups were considered as a whole there were significant differences between the control group and both the obese and elderly groups, for AUC and clearance values (table XVI).

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TWO GABA MECHANISMS FOR SPINALLY-MEDIATED ANTINOCICEPTION: EVIDENCE FROM ANTAGONISM OF 5-HYDROXYTRYPTAMINE BY BICUCULLINE

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5-Hydroxytryptamine (5-HT) is one of the neurotransmitters released in the spinal cord from axons originating from neurones in the brainstem; it is believed to be responsible for antinociception caused by electrical stimulation of the brainstem raphe nuclei [1]. We have demonstrated in our rat model using electrical current threshold for pain (ECTP) that intrathecal 5-HT produces segmental analgesic effects by combination with spinal cord 5-HT receptors and that an opioid pathway is involved [2]. The present studies were designed to determine if another propriospinal system, the GABA system, is also involved in this analgesia.

ECTP in the skin of the tail and neck was measured in rats with chronically implanted lumbar subarachnoid catheters. The rats were allocated randomly to two groups to receive either 5-HT 1.65 µmol (5 µl) or midazolam 46 nmol (10 µl) as the agonist. The responses to agonist alone and to intra-

TABLE XVI. *Area under the curve to infinity* (AUC_0^∞), *elimination half-life* ($T_{\frac{1}{2}}$), *plasma clearance* (Cl) *and volume of distribution* (Vd) *for the two diazepam formulations in the three groups. Mean* (SEM). *$P < 0.05$; **$P < 0.01$ *compared with control*

	AUC_0^∞ (ng ml^{-1} h)	$T_{\frac{1}{2}}$ (h)	Cl (ml min^{-1})	Vd (litre kg^{-1})
Control	3043.3 (393.3)	21.9 (3.4)	75.3 (7.4)	2.3 (0.4)
Obese	2038.3* (153.3)	26.8 (6.4)	127.9** (10.0)	4.2 (1.0)
Elderly	1833.3** (153.3)	34 1 (8.7)	124.1** (10.7)	5.7 (1.6)

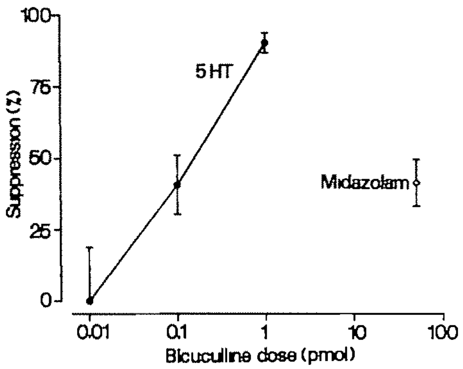

FIG. 7. Effect of bicuculline on suppression of the analgesic effects of 5-HT and midazolam.

thecal injections of agonist mixed with bicuculline 0.01–50 pmol were measured. The effect of bicuculline was calculated as percentage suppression of agonist response.

Both agonists produced segmental analgesic effects, but bicuculline given alone was without effect at the highest dose. Bicuculline did, however, produce dose-dependent suppression of the effects of both agonists, but at very different doses (fig. 7).

Two distinct propriospinal GABA systems exist, both involved in antinociception.

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RELATIVE EFFECTS OF INTRATHECAL MIDAZOLAM AND FENTANYL ON Aδ AND C REFLEXES

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In 1983 it was reported that midazolam could depress nociceptive reflexes when injected intrathecally (i.t.) in a dog model [1]. Recently it has been suggested that the antinociceptive effects of midazolam and fentanyl i.t. in rats are qualitatively different [2]. The present study was undertaken to determine the relative effects of these drugs on Aδ and C fibre pathways.

Studies were performed on 11 anaesthetized (alpha-chloralose 10 mg kg^{-1} h^{-1}), paralysed (suxamethonium 0.5 mg kg^{-1}/30 min) and artificially ventilated dogs. Temperature and blood-gas tensions were maintained within physiological limits. Radial, tibial and renal sympathetic nerves were exposed, desheathed and mounted on silver electrodes in mineral oil for stimulation and recording. Supramaximal electrical stimuli (duration 0.5 ms, intensity 30 V, frequency 0.33 Hz) were applied to the afferent nerves. Reflex sympathetic responses were displayed, averaged (16 responses), rectified and integrated. The dura was exposed by laminectomy to permit injection of drugs. Five preparations received midazolam 3 × 1-mg ml^{-1} increments i.t. followed by naloxone 2 mg i.v. and flumazenil 2 × 0 5-mg increments i.v. Six received fentanyl i.t. in doubling incremental doses from 2 to 64 µg in saline. Naloxone 2 mg was administered i.v.

Incremental i.t. doses of fentanyl abolished both Aδ and C reflexes and although midazolam also eliminated the Aδ reflexes, it depressed the C responses by only approximately 50 % from control. Naloxone i.v. antagonized the effects of fentanyl but not midazolam which was antagonized by flumazenil i.v. These results could explain differences between these two drugs on spinally-mediated analgesia and the clinical finding that midazolam i.t. interrupts somatic, but not abdominal visceral nociception where the C fibre input is greater [3].

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A TECHNIQUE TO ASSESS LARYNGEAL DAMAGE FOLLOWING TRACHEAL INTUBATION

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It is recognized that tracheal intubation may lead to damage to the vocal tract [1] but precise assessment of the impairment of vocal cord vibration secondary to intubation is lacking [2]. Existing methods of assessment of laryngeal function are not ideal and have practical limitations.

Adduction of the vocal cords interposes a barrier in the path of air flowing from the lungs. A pressure will build up in the trachea against the underside of the vocal folds. A point is reached when the cords open, allowing air to flow momentarily into the pharynx. This release of pressure results in the return of the vocal cords to the closed position and the cycle is repeated. In this way the larynx converts unidirectional air flow from the lungs into a series of puffs of air at a frequency which is determined by the physical conditions present in the larynx. The frequency of glottic cycles is responsible for voice pitch. A non-invasive test of laryngeal function has been developed which measures the precision of control of laryngeal pitch.

A normal laryngeal trace is characterized by regular pulses which correspond to the laryngeal impulse (opening and closing). The intervals between successive laryngeal pulses is measured using a microcomputer. The distribution of these intervals is plotted using a Bruel–Kjaer 2032 signal analyser.

We studied patients who were expected to undergo mechanical ventilation for a short period of 8–12 h after operation following vascular surgery.

A preoperative voice recording was made; the patient was asked to sing a note for 5 s and this was recorded on a portable tape recorder. When the patient was awake and the trachea had been extubated in the intensive therapy unit, the voice recording was repeated.

We found that after operation there is an increased variability of laryngeal pitch; this is seen as widening of the distribution of intervals between successive laryngeal impulses. This technique appears to be practical and may be used in the intensive therapy unit, and patients have found no difficulty in performing the test.

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FRESH GAS FLOW REQUIREMENTS OF A NEW ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEM DURING SPONTANEOUS VENTILATION

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Enclosed afferent reservoir (EAR) breathing systems are modified Mapleson A systems with an enclosed reservoir assembly on the inspiratory limb and a one-way expiratory valve. Recently Bruce and Soni [1] have shown that a fresh gas flow between estimated alveolar ventilation ($\dot{V}_A$) and minute ventilation ($\dot{V}_E$) is adequate in preventing rebreathing using an EAR. The aim of this study was to confirm these findings in a new EAR developed by Ohmeda, and to determine the fresh gas flow required to prevent clinically significant rebreathing as determined by the criteria of Kain and Nunn [2].

Twelve adult patients, aged 19–78 yr and ASA status I and II were anaesthetized with propofol before insertion of a laryngeal mask airway. Anaesthesia was maintained with 66% nitrous oxide in oxygen and 1–2% isoflurane or enflurane vol/vol. Fresh gas flow ($\dot{V}_F$) was initially set at 100 ml kg^{-1} min^{-1} to allow stabilization of the breathing pattern. After a period of 10–20 min $\dot{V}_F$ was progressively reduced until rebreathing occurred according to the criteria. Ten minutes was allowed for stabilization at each $\dot{V}_F$, before measurement of $P_{E'CO_2}$ using a mass spectrometer (Ohmeda MGM 6000). $\dot{V}_E$ was measured using both a Fleisch pneumotachograph and a flow transducer linked to an Ohmeda 7800 series ventilator.

Table XVII shows the minimum fresh gas flows used for all patients in the study. Rebreathing occurred when the $\dot{V}_F : \dot{V}_E$ ratio was less than 0.7. This occurred in seven of our 12 patients at $\dot{V}_F$ values of between 32 and 50 ml kg^{-1} min^{-1}.

These results indicate that the fresh gas flow requirement of the Ohmeda EAR system during spontaneous ventilation is similar to that for other modifications of the Mapleson A.

ACKNOWLEDGEMENT

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TABLE XVII. *Lowest flow rates used in 12 spontaneously breathing patients. *Indicates significant rebreathing as defined by Kain and Nunn*

Patient	$\dot{V}_F$ (ml kg^{-1} min^{-1})	$\dot{V}_E$ (ml kg^{-1} min^{-1})	$\dot{V}_F/\dot{V}_E$	change in $P_{E'CO_2}$ (kPa)	$\dot{V}_E$ (% change)
1	70	69	1.23	−0.13	0
2	50	66	0.88	0.53	−17
3	50	74	0.66	0	35*
4	70	50	1.44	0.13	8
5	50	122	0.41	0.53	32*
6	50	123	0.38	−0.4	41*
7	40	76	0.50	−0.53	66*
8	70	40	1.75	−0.27	−18
9	70	57	1.22	0.8	−2
10	33	51	0.65	0.4	60*
11	32	55	0.57	0.27	34*
12	55	113	0.48	0	13*

POSTOPERATIVE HYPOXAEMIA FOLLOWING MAJOR ABDOMINAL VASCULAR SURGERY: A PREOPERATIVE AND POSTOPERATIVE STUDY USING PULSE OXIMETRY

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Severe hypoxaemia following upper abdominal surgery may continue into the late postoperative period [1]. Previous studies have relied on discrete arterial samples being inter-

TABLE XVIII. *Percentage of preoperative (Pre-op.) and first five postoperative nights spent at less than 90% saturation*

		Postoperative night				
	Pre-op.	1	2	3	4	5
Median	0.55	0.75	19.5	46.2	16.7	2.3
Range	0–42.7	0–83.6	0–95.2	0–100	0–87.0	0–71.0

mittently drawn and analysed. However, the advent of pulse oximetry and computerized data collection has made it possible to sample continuously and hence detect the severity and duration of the troughs in oxygen saturation (Sa_{O_2}) after operation. In addition, the percentage of time that patients remain at or below any chosen value of arterial oxygen saturation can be measured. The aim of the present study was to ascertain the baseline values of arterial oxygen saturation occurring before operation and during the first five nights after operation following major elective abdominal vascular surgery, and to determine the percentage of each night that saturation was less than 90%.

Sixteen male and two female patients were included in the study (age range 30–80 yr). Data points for both Sa_{O_2} and heart rate were sampled once every 1 s from an Ohmeda 3700 pulse oximeter into a portable computer on one night before operation and for the first five nights after operation. Using a programme designed for respiratory sleep studies, data were analysed to derive the mean overnight Sa_{O_2} value and the 30-min period of least saturation for each of the study nights. In addition, we were able to assess the percentage of each night that patient's arterial oxygen saturation remained at <90% and <85%. Patients were premedicated with papaveretum and hyoscine and anaesthesia was induced with thiopentone and fentanyl 3–6 μg kg^{-1}. Maintenance was with 67% nitrous oxide, a volatile agent and incremental fentanyl. After operation, patients spent normally one night in ITU, the trachea being extubated once the patient was warm and cardiovascularly stable. Subsequent nights were spent on a surgical ward.

Postoperative analgesia was obtained with papaveretum 15–20 mg i.m. 3–4 hourly on demand. Oxygen was administered for the first two nights and often for the third night after operation, although its delivery to the patient was sometimes intermittent.

Values of arterial oxygen saturation were often low, with the minimum occurring on postoperative nights 2 and 3, when 50% and 53%, respectively, of the patients studied on these nights had overall mean Sa_{O_2} values of less than 90% saturation. Eighteen patients were studied on night 2 (median Sa_{O_2} 89.8%; range 85.3–97.3%) and 17 on night 3 (median Sa_{O_2} 89.9%; range 81.8–97.1%). The Sa_{O_2} values for the 30-min period of least saturation were also low, with five of 18 patients on night 2 and four of 17 patients on night 3 spending at least one 30-min period at less than 80% saturation. Even on night 5, two of 13 patients still had mean overnight Sa_{O_2} values <90% and four others spent at least one 30-min period at less than 90%. The percentage of the night spent at less than 90% saturation was also greatest on night 3 (table XVIII).

Five patients (28%) spent more than 25% of night 2 or night 3, or both nights, at <85% saturation. After operation, one patient required re-ventilation after night 3, four patients developed clinical signs of a chest infection or severe atelectasis and four patients became clinically confused during or after nights 2 and 3. Confusion appeared to be associated with prolonged periods of severe hypoxaemia. Patients spending >10% of either night 2 or 3 at ≤84% saturation had a significant risk of also being confused ($P < 0.01$, Fisher exact test).

After major abdominal vascular surgery, patients are at risk of spending prolonged periods during the night at saturation values less than 90% and often less than 85%. This is especially likely on nights 2 and 3. The role of this degree of sustained hypoxia in the development of postoperative myocardial infarction, arrhythmias, heart failure or confusion remains to be defined.

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INFLUENCE OF LOW-DOSE NALOXONE INFUSION ON HYPOTHALAMO-PITUITARY-ADRENOCORTICAL ACTIVITY

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I.v. infusion of naloxone has been used to attenuate the side effects of opioid drugs administered extra- or sub-durally [1]. This study assessed the effects of an i.v. infusion of naloxone 1 μg kg^{-1} h^{-1} on analgesia and hypothalamo–pituitary–adrenocortical (HPA) activity following intrathecal (i.t.) administration of diamorphine to postoperative patients.

We studied 27 patients of ASA status I and II undergoing lumbar laminectomy before mid-day. The patients were allocated randomly to receive equal volumes of saline ($n = 14$) or naloxone 1 μg kg^{-1} h^{-1} in saline ($n = 13$). The infusion commenced at the start of surgery and continued until the first request for analgesia after operation. Patients were anaesthetized using a standard anaesthetic technique. Each patient received diamorphine 0.015 mg kg^{-1} i.t. under direct vision just before wound closure. Serial blood samples were drawn before operation, before opioid administration, and at 20, 40, 60, 120, 240 and 360 min and 24 h after opioid administration. These were assayed blind using the YSI glucose analyser and radioimmunoassay for blood glucose and serum cortisol concentrations, respectively. Analgesia was assessed by visual analogue scoring at 1, 2, 3, 4, 8, 12, 16 and 20 h after operation by a blinded observer. Subsequent analgesia was provided by morphine i.m. on demand; the duration from operation to the first request for analgesia, and the dose required in the first 24 h after operation were observed. The occurrence of nausea, urinary retention and pruritus was noted. Results are presented as mean (SD). Statistical analysis was by ANOVA, Fisher's exact probability test and the Mann–Whitney *U* test.

Pain scoring by the patients was greater at 3 and 4 h after operation in the naloxone group compared with the saline group ($P < 0.05$). The requirement for morphine was 28 (13) mg and 25 (15) mg in the naloxone and saline groups, respectively.

Both groups of patients showed an increase in both blood glucose and serum concentrations of cortisol during operation. Further increases occurred after operation in the saline but not the naloxone group. At 40, 60, 120 and 240 min after i.t. injection, serum concentrations of cortisol were less in the naloxone group compared with the saline group ($P < 0.05$). Similarly, blood glucose was less in the naloxone group compared with the saline group at 4 h after operation ($P < 0.05$). No significant differences occurred in the incidence of side effects between the groups.

This study provides evidence of an increase in pain perception and a decrease in HPA activity following the use of a low-dose naloxone infusion in postoperative patients who have received diamorphine i.t. The reduction in HPA activity may be explained by the selective mu antagonism of naloxone at low concentrations [2].

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British Journal of Anaesthesia 1990; **65**: 594–597

CORRESPONDENCE

REGIONAL ANAESTHESIA IN PORPHYRIA

Sir,—We read with interest the case report from Drs McNeill and Bennet [1] on the use of regional anaesthesia in a patient with acute intermittent porphyria (AIP). We have dealt recently with an obstetric patient with the same diagnosis.

The patient was a 28-yr-old primagravida in whom AIP had been diagnosed 3 yr previously. In the past, acute crisis had consisted of vomiting, headache and, infrequently, left sided paraesthesia without residual neurological impairment. Her antenatal course was uneventful, other than mild non-proteinuric hypertension in the later stages of the last trimester.

She was seen at 38 weeks gestation by the Consultant Anaesthetist in charge of obstetric anaesthesia, with a view to discussing anaesthetic and analgesic management during labour. The patient at this consultation requested an extradural block for intrapartum analgesia. We found discussion with the Porphyria Research Unit in Glasgow extremely helpful during our assessment. Senior Medical staff in this unit were able to give us excellent advice on the possible safe and unsafe anaesthetic and analgesic regimens for this condition. We were therefore able to write an anaesthetic plan for this lady into the notes long before her admission in labour and to confirm that a regional block with bupivacaine would be safe.

The patient was admitted at term in early spontaneous labour. Soon after admission standard lumbar extradural block was instituted using 0.25% plain bupivacaine 10 ml with good analgesic effect. An infusion of 10% glucose was used during labour in order to prevent any tendency to hypoglycaemia which may have precipitated acute porphyric crisis. In the later stages of labour, a top-up dose proved ineffective and, on inspection, the catheter had migrated out of the extradural space. During the second stage, fetal distress ensued and a low spinal block utilizing 0.5% hyperbaric bupivacaine 1.5 ml was instituted for forceps delivery. Syntocinon was used rather than the ergot derivatives for management of the third stage. The mother's and infant's subsequent courses were uneventful. There was no evidence of maternal neurological impairment or any other evidence of acute porphyric crisis in the postpartum period until discharge at 5 days after delivery.

This case parallels McNeill and Bennet's findings of the safe use of regional block in porphyria in obstetric practice. We would emphasize the importance of thorough early antenatal assessment of the patient in order that the serious anaesthetic implications of this metabolic disorder can be appreciated. It is essential that an analgesic and anaesthetic plan is written into the patient's notes so that in an emergency situation (such as cord prolapse) the duty anaesthetist can deal with the situation swiftly and safely. We would commend readers to refer to a specialist in this field of metabolic medicine, as recommended by Walters and De Swiet [2]—in this case the Porphyria Research Unit (address and telephone number provided in the British National Formulary [3]).

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J. A. Halfacre
S. D. Woods
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SURVEILLANCE AND SAFETY

Sir,—Subsequent to two papers on non-experimental surveillance studies [1, 2], accompanied by an editorial [3] on the safety of atracurium, Dr R. K. Mirakhur [4] questioned the conclusions of the editorial and pointed out some relevant differences between the opinions of the authors of the surveillance studies and the clinical experience related to adverse effects secondary to the histamine-releasing potential of atracurium. We share Dr Mirakhur's opinion in the above matter; however, in addition to his remarks, we would like to point out the following.

Medical records often underestimate the frequency of common minor events such as mild cutaneous reactions. On the other hand, unusual and unexpected events will probably be reported in more detail. A comparison of *the number of events* reported when using two different drugs can become seriously biased because of this.

There are, however, further important sources of error. Patients who have a history of histamine-mediated allergy have most probably been administered, instead of atracurium, another neuromuscular blocking drug that is believed not to have a tendency to liberate histamine. For this reason, histamine-mediated reactions observed in a large scale surveillance, might appear to be associated more frequently with other drugs. This type of error in surveillance studies might severely bias the outcome, particularly when the incidence of adverse drug reactions is being compared. Therefore, the data from the two surveillance studies [1, 2] cannot be considered as evidence for atracurium's being as safe, or even more safe, than other drugs from the same class of agents.

Similar sources of error escaped the attention of both Professor Hull [3] and Dr Mirakhur [4] in an Australian prospective surveillance study [5] in which atracurium, compared with alcuronium, was found to be a safer drug based on the frequency of adverse reactions observed. This, however, cannot be interpreted as evidence that atracurium is as safe as *other* neuromuscular blocking drugs. Atracurium, in spite of being associated with serious events less frequently than alcuronium, may still cause serious adverse reactions more frequently than other neuromuscular blocking agents.

The main information about atracurium that can be extracted from the data gathered in the U.S.A. [1], Great Britain [2] and Australia [4] seems to be that the drug has been given at 3346 events without having caused any life-threatening serious adverse reactions attributable to the drug. This evidence may be used to form a 95% confidence interval for the risk of a life-threatening serious adverse reaction under the circumstances studied. The risk may be judged to be less than 9 in 10000. This is in agreement with earlier clinical studies [6, 7] which have shown histamine release to be a generic feature of isoquinoline compounds [8, 9]. Such risks should be considered when selecting the drug to use.

L. I. Eriksson
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Linkoping

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A USER-FRIENDLY DISCONNECTION ALARM

Sir,—A recent editorial [1] reviewed the progress towards an International Consensus on Monitoring and one of the items the editorial considered to be essential was a pressure alarm warning of disconnection within the breathing circuit of a patient undergoing artificial ventilation of the lungs. During the past year we have been using a simple "user-friendly" alarm which has several unique features that have made it a useful addition to monitoring during cardiac and thoracic surgery.

The major advantage in the design of the Rutter alarm* is its automatic switching-on facility when a pressure pulse is detected. This entails that the alarm is always connected to the ventilator circuit and it is never necessary to switch it on. During cardiopulmonary bypass, artificial ventilation of the lungs is discontinued and the alarm is then silenced by pressing the on/off button for a period of 1 s. When ventilation is recommenced, the alarm automatically switches on again with the first positive pressure cycle in the airway.

The alarm function is arranged sensibly with a flashing red LED and a soft tone for 15 s which increases to a full and penetrating volume. A conventional mute button is provided also which mutes the sound signal, but not the flashing LED, for a period of 2 min. The electronic circuitry is arranged so that a delay of 0.7 s below, and 0.35 s above the cycle pressure is required for detection as a valid pressure wave form. This is invaluable when using ventilators of a Manley type, as the transient pressure wave form which may be produced when the patient is disconnected from the circuit is rejected and not regarded as a valid pressure cycle. There are drawbacks as with any pressure sensing device. It is unable to detect a partial disconnection resulting in a leak if a detectable pressure cycle is still produced and, because the cycling switch is set in the range of 5–7.5 cm H_2O, it cannot be used with PEEP values greater than that.

The alarm has been reliable and has not needed new batteries, despite instruction to change them yearly, and only the off control seems to be used. The controls are self-explanatory and the device can be recommended as a simple, inexpensive device to give additional monitoring of artificial lung ventilation.

D. W. Bethune
A. Burns
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REFERENCE

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*The alarm is available from G. Rutter Limited, "Kaimosi", Pyle Hill, Woking, Surrey GU22 0SR.

I.V. INFUSIONS OF MORPHINE AND REGIONAL ANALGESIA BY EXTRADURAL BLOCK

Sir,—The study of Clyburn, Rosen and Vickers [1] draws conclusions that are scarcely warranted by the limited data presented.

In this study, three of the four patients who received i.v. morphine had ectopic ventricular beats, and in one of these patients there were 163 in the observation period, which was presumably for about 24 h. In contrast, only two of the four patients studied during extradural analgesia had ectopic beats, and these were very rare. Interpretation of these data is difficult. No details were given of the cardiac status (or even the general health) of the patients before operation. No measurements were made of the incidence of ectopic beats before surgery, particularly during sleep. Consequently, it is not clear if the patients in the two groups were comparable, or if the incidence of ectopic beats had increased after the surgery. The groups were compared with a test that used the actual number of ectopic beats as a "score" for each individual. Although a valid means of comparison, such a test exaggerates the statistical, in comparison with the clinical, differences between patients. For example, 163 ectopic beats in 24 h is, on average, a rate of one ectopic every 9 min or so: not a rate that would be likely to lead to clinical concern.

A clinically relevant comparison of the groups would have been to examine the number of patients in whom the rate of ectopic beats had increased by an appreciable amount after surgery. A doubling of the rate might have been chosen arbitrarily as important. This comparison supposes that ectopic ventricular beats are clinically important, although present opinion suggests that this may not be so in the previously healthy heart [2]. Such a comparison would naturally require a greater number of patients to be studied than were reported in this study.

The method that was used to assess the incidence of obstructive apnoea depended upon an external sensor which compared the motion of the suprasternal notch with that of the sides of the abdomen. This method has not been validated by comparison with a method that is likely to detect airway obstruction reliably, such as the combination of oesophageal pressure (to assess ventilatory effort) and a sensor to assess gas flow. Because there are likely to be substantial differences in ventilatory movement in patients before and after abdominal surgery, validation of the method in the circumstances of the study would be necessary before the signal could be interpreted reliably. For example, it is clear that abdominal motion in patients after abdominal surgery is reduced [3] and that it is altered by extradural analgesia with 0.5% bupivacaine [4]. Abdominal pressure changes with breathing can be very variable, from breath to breath, in patients after abdominal surgery [5]. Changes in posture cause considerable alterations in the motion of the chest wall [6]. The authors themselves refer in discussion to the inevitable displacement of probes, and suggest that, as they obtained overall results similar to those of others [7], the incidence of false results might be small. In fact, the incidence of possible obstructive apnoea reported in this study for patients receiving morphine was considerably less than in the study of Catley and colleagues [7], by a factor of at least five times. Without a separate, simultaneous method of assessment, how are the authors able to suggest, as they do, that the apparatus used was efficient in the detection of apnoeic events?

The work of Catling and colleagues [8] is quoted in association with a statement that sudden death may result from cardiac arrhythmia induced by hypoxaemia. This suggests that, in the work quoted, sudden death was related to these potential predisposing events. This is not the case: in the study to which reference is made, measurements were made of ventilatory movements in patients after operation. There were no measurements of cardiac rhythm, or of oxygen saturation, and there were no deaths.

It is only by reference to the study of Catley and colleagues [7] that the inference is made that obstructive apnoea can cause hypoxia. Because, as the authors of the present study note, subsequent work has shown that oxygen therapy can prevent such hypoxia [9], it would be relevant to know if oxygen was administered to the patients in this study. If not, it would appear that the investigators chose to conduct the study in a way that might exaggerate the group differences but not provide the best known treatment for their patients.

Many anaesthetists suspect from clinical observation that extradural analgesia is better than i.v. opioid, in terms of less respiratory depression and airway obstruction. Unfortunately, the proof of this suspicion is not provided by this study. Only with a greater number of subjects, and use of validated methods with known reliability and sensitivity in the population to be studied, can this possibility be tested properly.

G. B. DRUMMOND
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Sir,—Thank you for the opportunity of replying to Dr Drummond's letter. The patients we studied were ASA I or II; none had any history of cardiac disease. A period of prolonged preoperative ECG monitoring might have been useful in assessing any increase in the incidence of ectopic beats; however, preoperative 12-lead ECG in the patients studied were all normal. Patients were also allocated randomly to the two treatments to reduce bias.

We used the absence of air flow at the nose (measured by carbon dioxide detection) as the main indicator of apnoea. Dr Drummond criticizes the use of the modified Graseby apnoea alarm for assessing ventilatory movements. The modified monitor was used only to give additional qualitative information about the presence or absence of ventilatory movement, to enable us to differentiate between central and obstructive apnoea.

Catley and colleages [1] detected an average of 18 obstructive apnoeas per 24 h in 16 patients receiving morphine, with a wide variation between patients, and this is similar to our detection rate of 13 apnoeas per patient each 24 h. This difference is clearly not a factor of five times!

When clinically indicated, oxygen is administered to our patients after their discharge from the recovery ward. No one in this low risk group of patients was prescribed oxygen. Furthermore, the study was conducted before the general availability of pulse oximetry.

We agree that our study is small, but nevertheless it is an important indicator of the potential hazards of i.v. opioid medication. We agree with Dr Drummond that more extensive investigation is necessary.

P. A. CLYBURN
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REFERENCE

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INTRAOPERATIVE MONITORING

Sir,—The editorial on monitoring by Winter and Spence [1] cites an article by Westhorpe [2] on "Ergonomics and monitoring". This was a very general article and the layout of physiological variables was only a proposal. The concept that the magnitude of each variable could be represented by points on a series of lines all of equal length (representing the range of each variable) has been described before in a working system [3].

One drawback of Westhorpe's proposed circular display is that it has no "historical" content; it would be difficult to present the display in a trend format. Anaesthesia is a "real-time" medical discipline and thus it might be considered that, apart from medico-legal reasons, the value of physiological variables more than 15 min old is minimal.

The display in the working system was a series of histograms disappearing to a distant horizon, the most recent values being represented by an array of histogram blocks at the front of the display. Acceptable limits for the variables was a constant width band across this array, so that any deviation from the acceptable limits was represented by a hill or valley in the three-dimensional display

I agree with Westhorpe's views on the need for grouping of monitored values in such a way that the number of alarms is minimized. Two alarms, one for the patient variables and one for the anaesthetic delivery system, would lead through a branching fault-finding algorithm to a definition of the exact nature of the alarm.

Anaesthesia is well behind schedule for a quantum leap in the design of both an ergonomic anaesthetic delivery system and an ergonomic "intelligent" monitoring system.

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Sir,—Whilst agreeing that Westhorpe's method of monitoring does not provide for any permanent method of record keeping, it was our intention in this editorial merely to draw attention to the possibility of developing this as a more ergonomically designed "user friendly" method of intraoperative monitoring.

A. W. WINTER
A. A. SPENCE
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British Journal of Anaesthesia 1990; **65**: 598–601

BOOK REVIEWS

Regional Anesthesia: An Illustrated Procedural Guide, 1st Edn. By M. F. Mulroy. Published by Little Brown & Co., Boston, Toronto, London. Pp. 289; indexed; illustrated. Price £29.95.

In the past few years there have been several new textbooks on regional anaesthesia and the first reaction is to ask if there is a place for another one. However, this new book has much to commend it, particularly as it is written primarily by a single anaesthetist; only one of the 22 chapters, and that on the very specialized field of paediatric anaesthesia, was written by another person. The principal author, Michael Mulroy, works at the Virginia Mason Clinic, Seattle—a hospital renowned for regional anaesthesia, having included among its staff Daniel C. Moore, the Bridenbaugh brothers and Gale Thompson. It is not surprising, therefore, that the book contains a wealth of knowledge and practical experience which the author conveys lucidly to his reader.

The first five chapters consider the basics of the subject and provide an excellent grounding; they are clear, concise and well illustrated. The complex subject of local anaesthetic action is made relatively simple and there are some interesting explanations for strange clinical phenomena, for example why an area numb to pinprick may still perceive a skin incision as partially painful, and core and mantle effects explaining early motor block in brachial plexus anaesthesia.

The next 14 chapters are descriptions of the various block techniques and, again, the author has managed to achieve considerable detail in admirably brief accounts. This is helped by excellent, simple black and white line drawings with nerves being illustrated in yellow.

The book concludes with three chapters examining the particular problems of obstetrics, paediatrics and pain management. The obstetric anaesthesia chapter contains information necessary for safe practice of regional anaesthesia for the parturient, but there is scant consideration of intrathecal and extradural opioids. It is not clear if this relates to the delay in publication or is actually a reflection of the opinion of the author on their usefulness. There is a suggestion that the book was in preparation for a long period, as the benzodiazepine antagonist flumazenil is described as awaited and the increasingly popular peribulbar block for ophthalmic anaesthesia is not mentioned.

The chapter on paediatric regional anaesthesia is written by an acknowledged expert in the subject, but I was surprised that there was no description of lumbar extradural analgesia, as it is now very popular for postoperative analgesia in this age group. The final chapter on pain management includes considerations of acute and both benign and malignant chronic pain and succeeds in defining succinctly the problems involved and the methods of treatment.

In his preface the author states that the book is a "practical manual meant to be taken to the operating room to show how to do the common regional techniques". I feel that it fulfils this aim admirably, and I would recommend any trainee to read it before performing any of the regional techniques described and before appearing at the examinations. The book is good value for money, although the soft covers and spiral binding may reduce its durability. Some of the illustrations have extensive legends and the figures do not always appear close to the portion of the text to which they refer. However, these are small criticisms of an excellent book that has fully justified the aims and efforts of its author.

A. Rubin

Manual of Pediatric Anesthesia, 3rd Edn. By D. J. Steward. Published (1990) by Churchill Livingstone, Edinburgh. Pp. 455; indexed; not illustrated. Price £22.50.

The 3rd edition of David Steward's *Manual* appears 5 years after the 2nd and 10 years after the 1st edition. The task of keeping the text up to date has transferred from the Hospital for Sick Children in Toronto to the Department of Anesthesia at British Columbia's Childrens' Hospital, with little or no evidence of editorial alteration; in spite of several contributors, the style throughout is even.

The structure of the book remains unchanged. Foundations of Pediatric Anesthesia is a concise and clear review of the pertinent physiology, pharmacology and technology associated with paediatric anaesthesia; unfortunately in this section, unlike the remainder of the book, some of the references are a little dated.

The section "Anesthesia for Specific Procedures" informs the more experienced about complex cardiac, neuro- and neonatal anaesthesia and contains invaluable information for the occasional paediatric anaesthetist faced with a child presenting for minor surgery such as circumcision or with minor trauma.

The final section contains three appendices, the first of which is the well known list of syndromes associated with paediatrics and their anaesthetic significance; the second is a useful pharmacopoeia with appropriate doses for paediatric patients; finally, there is a useful appendix on resuscitation.

There are several typographical errors such as "fantanyl"; Philip Ayre was reported to have published his article on the T-piece in 1973, although the reference was correct (1937). There is an unexplained change from the previous edition in the doses of lignocaine for bronchoscopy—from 3 mg kg^{-1} to 5 mg kg^{-1}, although the reviewer prefers the smaller dose in this situation. It is also the reviewer's experience that rigidity may be a major problem in the very young following fentanyl and that this is not particularly rare. Some British anaesthetists might find it unacceptable to avoid premedication because the ophthalmologist wished to examine the eyes immediately before anaesthesia.

A less minor quibble is that of the steadfast refusal of many North American authors to grasp the nettle of S.I. units; consequently this book may lose its popularity unnecessarily among the present generation of young European anaesthetists.

My complaints are few and minor. This *Manual* remains at the top of my list of the many current paediatric anaesthetic textbooks available, not only because it is almost certainly the best value for money, but also because it should be consulted by all anaesthetists whether specialist or occasional paediatric practitioners.

D. S. Arthur

Anesthesia for Vascular Surgery, 1st Edn. Edited by M. F. Roizen. Published by Churchill Livingstone, New York. Pp. 486; indexed; illustrated. Price £55.00.

In his preface, the editor notes the absence of a major textbook devoted to the science and clinical practice of anaesthesia for major vascular surgery. He clearly intended to fill this void with this 486-page, multi-author first edition.

A total of 32 contributors were recruited for the 32 chapters contained in this volume. Despite an understandable bias towards contributors from the author's own institution, the University of Chicago Pritzker School of Medicine, other contributors included such well recognized authorities as David Cullen, Joel Kaplan, Philip Larson, Denis Mangano, John Michenfelder, Fredrick Orkin and Nathan Pace. A number of especially sound, thorough and well written chapters featured young authors such as Ira Isaacson, Michael McCaffrey and Mark Yaeger.

The text is organized conveniently to cover six broad categories of knowledge and clinical practice: scope of the problem; anaesthesia and surgery for cerebrovascular insufficiency; surgery for visceral ischaemia and suprarenal aortic reconstruction; surgery for abdominal aortic reconstruction; surgery for peripheral vascular insufficiency of the lower extremities; controversies and other issues.

Section I deals with the scope of problems involved in providing anaesthesia for patients presenting for major vascular surgery. This section includes a very impressive contribution from Richard Glasser outlining the factors affecting patient outcome following carotid endarterectomy and abdominal aortic surgery. Unfortunately, the other contributors in this section—Orkin and Teplick and others—addressing the issues of morbidity following anaesthetic procedures in the perioperative period and monitoring devices for vascular surgery, made little attempt to confine their contributions to the issues under consideration and included such essentially irrelevant topics as dental injury, pulmonary aspiration of gastric contents and awareness during anaesthesia. Very little effort was made to focus the discussion on limitations and correct functioning of monitoring devices in the context of patients presenting for major vascular surgery.

Sections II–V, dealing with anaesthesia and surgery for cerebrovascular insufficiency, visceral ischaemia and suprarenal aortic reconstruction, abdominal aortic reconstruction and peripheral vascular insufficiency, were preceded by welcome and informative contributions by vascular surgeons Robert Lusby and Christopher Zarins, who outlined the surgical techniques and special considerations in the management of these technically difficult and complex procedures.

In Section II—Anesthesia and Surgery for Cerebrovascular Insufficiency—the issues of indications for surgery, use of intraluminal shunts, evaluation of neurological function and monitoring for cerebral ischaemia, choice of anaesthetic technique, etc. were discussed fully by Roizen from Chicago, Larson from Stanford and Michenfelder from the Mayo Clinic. As each author outlined his own individual philosophy, experience and clinical practice, this approach invariably led to a significant overlap and repetition. Most of the contributors in this section outlined the rationale for the extensive North American use of processed and unprocessed EEG and regional cerebral blood flow measurements during carotid endarterectomy. The use of transoesophageal echocardiography and pulmonary capillary wedge pressure changes to detect myocardial ischaemia in patients undergoing carotid endarterectomy reflect Dr Roizen's personal expertise, but this hardly reflects current anaesthetic practice and is not very relevant for the average reader. Similarly, most U.K. anaesthetists will question the claim of Philip Larson that "the central venous catheter is very useful in virtually all patients undergoing carotid endarterectomy, both for monitoring of adequacy of fluid therapy and for administering vasoactive drugs quickly and safely."

The section on anaesthesia for abdominal aortic reconstruction outlines the anaesthetic patient management in such institutions as the Massachusetts General Hospital, Balor College of Medicine, Dartmouth Medical School, Stanford, in addition to the editor's own institution. This format again leads to considerable overlap and repetition, especially concerning the preoperative invasive and non-invasive cardiovascular assessment, the choice of anaesthetic technique, the haemodynamic changes associated with aortic cross clamp application and release, and postoperative complications. Whereas most of these contributions were considered well and the opinions were substantiated by published work, a notable exception in this regard was the contribution from Palm and Davidson from the Massachusetts General Hospital. In this case very little effort was made to substantiate the practice of administering 10–12 ml of 0.75% bupivacaine in the extradural space before induction of anaesthesia, the infusion of phenylephrine to keep arterial pressure within 10–20% of baseline and the average infusion of warm crystalloid 750–1000 ml h^{-1}.

Section VI—Controversies and Other Issues—comprises several informative and appropriate chapters concerning the role of two dimensional transoesophageal echocardiography during anaesthesia for vascular surgery, the appropriateness of pulmonary artery catheterization in patients undergoing vascular surgery and monitoring of EEG, and somatosensory evoked potential monitoring during major vascular surgery.

In summary, Dr Roizen has produced a first of its kind—an authoritative, balanced, well written and presented, indexed, referenced, illustrated text book of major vascular surgery. The apparent deficiencies, including some repetition and overstatement, are more than compensated by the wealth of clinical and scientific information presented. This first edition will, no doubt, be the first of many on this subject. In future editions, the editor may consider including a section on invasive and non-invasive assessment of cardiac function as a separate chapter, thereby avoiding repetition in many subsequent chapters. He should refrain from repeatedly citing work which appeared many years ago in abstract form and which has not subsequently been published.

The editor might temper his personal enthusiasm for transoesophageal echocardiography during carotid endarterectomy with a more balanced assessment of its current application. In addition, he should consider a contribution from outside North America to extend the scope of the text and to complement the North American contributions.

At last, an exciting new anaesthetic topic and an excellent reference text for every Department of Anaesthesia.

A. J. Cunningham

Manual of Cardiorespiratory Critical Care, 1st Edn. Edited by F. Guzman, A. Hedley Brown, M. Been, S. Cook, C. Wren and D. Richens. Published by Butterworths, Sevenoaks. Pp. 314; indexed; illustrated. Price £19.50.

This 300-page manual has six editors and 22 other contributors cited; consequently, it lacks consistency both in style and content. There are three sections covering cardiac disease and three on respiratory disease; the sections in each group deal with medical, surgical and paediatric considerations.

The editors are based in one of the larger cardiothoracic centres and the manual is therefore aimed at juniors working in this type of environment; there is less of value for those working in a general unit, with the exception of an excellent chapter on respiratory medicine. The surgical sections outline most of the operations undertaken, with useful information on pre- and postoperative management; the medical sections deal with problems which may be encountered in the ITU. Four of the sections close with aspects of appropriate nursing care; these make interesting reading for the medical practitioner, but one wonders if they are useful in a manual where the "emphasis is on practical instant help in acute situations".

Inevitably in a manual, statements are made without the "space" for qualification. However, the remark that preoperative infarction may be caused "by hypoxia, particularly in the anaesthetic room" caused this anaesthetist some consternation. Nevertheless, the book does contain much that is commendable; there are many useful tables, ranging from resuscitation algorithms, and doses of inotropes to causes of respiratory failure in neonates, with an excellent *résumé* of cardiovascular formulae in the section on cardiac surgery. In addition, there is a comprehensive index, which is essential for this type of publication.

G. W. Jones

Essentials of Anesthesiology, 2nd Edn. Edited by D. C. Chung and A. M. Lam. Published by Harcourt Brace, Jovanovich Ltd, Sidcup. Pp. 294; indexed; illustrated. Price £15.50.

This book was published first in 1983 and has been revised in this second edition to include areas of progress in anaesthesia. It is a North American text and is aimed principally at medical students and other trainees approaching the specialty of anaesthesia for the first time. The book consists of 25 short chapters which cover a wide spectrum of anaesthetic practice, from the history of anaesthesia and basic principles to a chapter on AIDS and the anaesthetist. The text is well written and easy to read. There are plenty of helpful and clear diagrams which the trainee will find instructive.

The contents cover the field of anaesthesia very well. Starting with a chapter on basic principles, the next five chapters concern drugs used in anaesthesia. There are three chapters on the anaesthetic machine, circuits, and ventilators, then the text moves on to the important areas of anaesthesia and the respiratory system, the effects of systemic illness and preoperative assessment. The chapter on monitoring principles is up to date and relevant to modern anaesthetic practice. The concept of basic intraoperative monitoring is discussed and the ASA standards are contained in the appendix.

Unfortunately, there is only one chapter for the wide field of obstetrics, paediatrics, geriatrics and ambulatory patients and these areas are, therefore, only briefly outlined.

Trainees reading this text will quickly gain an insight into the practice of anaesthesia and, in conjunction with practical experience in the operating theatre, will be encouraged to read further.

This book is priced competitively at £15.50 and can be recommended for students wanting one book to introduce them to the complex and challenging specialty of anaesthetics.

J. A. Langton

Pharmacology of Neuromuscular Function, 2nd Edn. By W. C. Bowman. Published (1990) by Wright, London, Boston, Singapore, Sydney, Toronto, Wellington. Pp. 316; indexed; illustrated. Price £45.00.

This book is as good an example as one could wish to find of a monograph. It gives the scientific background to the use of neuromuscular blocking drugs in anaesthesia. Too often, lip service is paid to the scientific study of anaesthesia; this book illustrates comprehensively that the principles we use to understand the physiology and pharmacology of the neuromuscular junction are built upon observation and on the subsequent generation and critical testing of hypotheses. Much has happened in the decade since the publication of the first edition: for example, we now know in considerable detail the structure of the acetylcholine receptor, about how it is synthesized, about how it can change its shape when it binds acetylcholine, and about how drugs interact with it. Equally, it has become possible to study the interaction of drugs with single receptors and to obtain some idea as to the molecular events. Bowman reviews the evidence critically and shows us the limitations of our knowledge as well as the newer theories.

As in the first edition, he begins with a chapter on striated muscle, then looks at excitable membranes in general and develops his main themes on looking at the physiology and pharmacology of the junction. He ends with a chapter on muscle contraction. All show his tremendous depth of knowledge and his ability to communicate even the most esoteric of topics.

This monograph is a must for anyone with an interest in the skeletal neuromuscular junction and should be compulsory reading for those talking about the basic sciences as applied to anaesthesia. It is a very important contribution to all our knowledge.

J. Norman

Electricity, Safety and the Patient. By J. M. Bruner and P. F. Leonard. Published by Year Book Medical Publishers, Inc., Chicago, London, Boca Raton. Pp 338; indexed; illustrated. Price £67.00.

This book describes basic electrical theory, the principles of electrical safety, the nature of electronic instrumentation, the electrophysiology of cardiac excitability and the history of electrical accidents in hospitals. Following chapters include the physiology and hazards of cardiac pacemakers and surgical diathermy, the Codes and Standards governing the design of electrical equipment, and the associated medico-legal issues.

The title suggests that this might be a rather tedious book. It is, in fact, nothing of the kind. More than that, it is quite remarkable in both style and content. Above all, it is a book which the authors wished to write and then *enjoyed* writing. Even readers who believe that electricity should be ignored so long as it works, could not fail to find it readable. It is written in a colloquial, enthusiastic and journalistic style which never leaves the reader in any doubt as to the authors' views. The text is scattered liberally with quotations (some quite long) from the literature, and is highly referenced. The referencing system is unusual, making use of both footnote and end-of-chapter references. At times this is confusing, but it has to be admitted that, on the whole, it works quite well.

There are a few problems. For instance, some sections do seem dated, perhaps because the authors have drawn heavily on their own published work. For instance, the essential features of single-ended and differential amplifiers are explained (and illustrated) in terms of valve amplifiers. The standard of illustration is variable. While some diagrams are well-drawn (and modern), many figures are taken from previously published articles by Dr Bruner. Some of them are quite old (1967), and it shows. Where such figures are of historical interest, such as original photographs of equipment and installations which no longer exist, it must be accepted that there is no alternative, but in many cases one feels that old diagrams and photographs have been used for convenience. Some are presented in cartoon form, and might have been quite amusing at the time.

The history of electrical accidents is superbly written, and should be read by every practising Surgeon and Anaesthetist. There is an excellent account of the development of electrical standards, together with pithy (and often scathing) comments on many of the personalities involved.

However, it is all *very* American. The book was written for the American market, and there are no allowances for unfamiliarity with American spelling and technical jargon. There is no mention of voltage supplies other than 120 v, and there is no mention whatever of such organizations as the International Electrotechnical Commission or the British Standards Institute. Indeed, the international standards scene is ignored altogether.

No matter. It is, in its own terms, quite comprehensive, well indexed and highly educational. In the great majority of cases the authors' views correspond with those of the reviewer, and even where they do not it is still an excellent read.

C. J. Hull

Ostlere & Bryce-Smith's Anaesthetics for Medical Students, 10th Edn. By T. B. Boulton and C. E. Blogg. Published (1989) by Churchill Livingstone, Edinburgh, London, Melbourne and New York. Pp. 271; indexed; illustrated.

The last textbook of anaesthesia I reviewed came in two volumes and needed considerable strength to lift onto a desk. This book is much smaller and could even fit into a white-coat pocket. It is, of course, designed for a different readership. It is the 10th edition of a classic introduction of anaesthesia to medical studients. Dr Ostlere's distinguished contribution to anaesthesia has passed into new hands and it is right that both maintain the link with the Nuffield Department at Oxford. Does it remain a readable book which can be recommended to medical students?

It is concerned principally with anaesthesia, and is divided into two main sections. The first defines the essential components of using drugs to alleviate pain and the necessary concomitant actions of general anaesthetics in producing unconsciousness. The second part gives a simple and lucid account of the practical aspects of anaesthesia and emphasizes the need for safety.

A final chapter covers cardiopulmonary resuscitation, outlining and emphasizing what all young doctors should know of basic resuscitation skills, and introduces some of the more advanced techniques. Whilst I accept this need, I do think anaesthetists have more to offer in helping students learn to anticipate the need for resuscitation. Whilst the correct actions after a cardiac arrest may save a number of patients, in others the detection of hypoxia before the arrest may lead to a better outcome. Let us teach basic and advanced CPR, but also prevention!

The book does not go into areas such as the intensive care unit. A pity, as much of what goes on in such places can form excellent instruction in pathology, pharmacology, general clinical care and the important communication skills.

Despite these possible limitations, the book does achieve its aim of introducing the fundamental aspects of anaesthesia to medical students. Drs Bouton and Blogg are continuing a fine tradition. They also show that anaesthesia is enjoyable. They have kept some of the old anecdotes: the old ones are always the best.

J. Norman

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL I

AWARENESS AND MEMORY IN ANAESTHETIZED PATIENTS

In a previous editorial, Prys Roberts [1] defined general anaesthesia as a threshold event in which loss of conscious awareness occurs at a point where the ability to perceive pain and the ability to recall any subsequent events are lost. This view of anaesthesia, as an all-or-none phenomenon, differs from that of Jones and Konieczko [2], who considered anaesthesia to be a continuous spectrum in which increasing depth of anaesthesia passes through three broad levels of awareness. These range from conscious awareness with explicit recall, to conscious awareness with no explicit recall, to subconscious awareness with implicit but no explicit recall. It is not yet known if there is a stage of no awareness. This proposal embraces the concept of awareness as *pre-conscious processing of sensory information* [3] which may or may not subsequently enter consciousness where the information is subject to introspection. Thus with increasing depth of anaesthesia the brain may remain aware of events in the outside world, these experiences may be stored in long term memory (LTM), but the ability to recall those events from LTM into working conscious memory becomes progressively impaired.

The first of these levels corresponds to the normal conscious state which may occur by accident in an apparently anaesthetized but paralysed patient. The second of these levels was described by Russell [4] and by Schultetus and colleagues [5], who showed that apparently anaesthetized and paralysed patients are able to respond with an isolated arm to verbal commands presented during surgery, but after operation they have no explicit recall of this experience. This is consistent with the observations of Artusio [6], who showed that ether given in a concentration that did not interfere with a patient's ability to carry on a conversation during cardiac surgery did produce profound analgesia and amnesia. A deeper level of anaesthesia is implied when the concentration of anaesthetic in the brain prevents both the response by the isolated forearm and explicit recall; however, patients may remain susceptible to intraoperative suggestion and their subsequent postoperative course may be modified. This state of subconscious awareness depends upon implicit memory being formed under general anaesthesia. This leads to further consideration of the neuropharmacology and psychology of memory during general anaesthesia.

The anatomical basis for memory formation was proposed first in 1894 by Ramon and Cajal [7], who suggested that learning might produce prolonged morphological changes in the effectiveness of synaptic connections between nerve cells. Hebb [8] proposed a specific cellular mechanism whereby conjunctive activity in both the pre- and postsynaptic elements of a synapse would lead to the strengthening of that synaptic connection and hence to memory formation. This hypothesis has been confirmed repeatedly. The synaptic elements now known to be involved are both n-methyl D aspartate (NMDA) and non-NMDA receptors, but it is the NMDA receptor which endows synaptic transmission in the mammalian nervous system with special properties—allowing these receptors to play a key role in plasticity during development and learning. This special property is termed long term potentiation (LTP) which is a long lasting increase in synaptic efficacy which follows a brief stimulus train. LTP is known to develop in the hippocampus [9, 10] and this area is known to be involved intimately in memory storage. LTP therefore has been proposed as a mechanism for memory storage [11, 12]. There is no direct evidence to link LTP to memory formation in man, but animal experiments suggest that there might be such a link [13]. NMDA receptors are critical in the development of LTP and they may be antagonized by several compounds, which include phencyclidines such as ketamine and D amino-phosphovaleric acid (DAP5), *but not by conventional anaesthetics* [14]. Pearce, Stringer and Lothman [14] examined the effects of halothane, enflurane and isoflurane on synaptic transmission in the rat hippocampus *in vivo* and compared this with the effects of urethane and ketamine. The effects on NMDA-mediated neurotransmission were studied by using evoked responses and long term potentiation in the stratum pyramidale of CA1 with stimulation of the contralateral CA3 region. They showed that LTP was abolished by ketamine, whereas urethane and all the volatile agents in doses of 1.5–2.1 MAC had no effect on the development of LTP via an NMDA mechanism. However, the volatile agents did enhance inhibition as measured by a paired pulse technique. This might support the observation that volatile agents may not affect some stages of memory formation, and may help to explain the retention in implicit memory of intraoperative events by anaesthetized patients. However, there is clinical evidence that general anaesthetic agents have other amnesic effects [4–6] and Bentin, Collins and Adam [15] have also shown that subanaesthetic doses of enflurane affected significantly the ability to learn.

Cognitive psychologists divide the architecture of memory into short term and long term memory and emphasize that the type of memory system used determines how information is *encoded*, *stored* and *recalled*. Short term memory (STM) can be conceived as a *working memory* [16] involved in temporarily storing both speech related and visuo–spatial information currently in use. This interfaces with both the outside world and with LTM, the latter being an exceedingly large store which may itself be divided into *procedural* and *declarative* memory. Procedural memory is manifested in overt skills or the recall of information not dependent upon conscious retrieval (e.g. remembering how to ride a bicycle, or drive car). Declarative memory has been divided further into *episodic* and *semantic* memory [17]: episodic memory relies upon conscious recall of specific life events and episodes (the day when my father died), whereas semantic memory contains information about the world and language and is dissociated from the circumstances in which the information was acquired. It is important to note that the retrieval of knowledge from semantic memory and skills held in procedural memory represent *implicit* and effortless expressions of memory, whereas *explicit* retrieval from memory needs a conscious, effortful, recollection of events [18, 19].

It is likely that the learning mechanisms involved in implicit and explicit memory are different, although both run in parallel in LTM. Explicit memory requires specific attention at the time of learning and in this way new associations and new memories are formed [20]. Implicit learning is essentially an automatic process, with the strengthening of existing associations within LTM rather than formation of new memory [21]. This process does not need attention, and may be akin to the effects of subliminal stimuli which are capable of entering subconsciousness and subsequently affecting behaviour. [3].

Kihlstrom and Schacter [22] have suggested that general anaesthesia causes dissociation between explicit and implicit memory. Levinson [23] was one of the first to examine the possibility of subconscious awareness in apparently adequately anaesthetized patients. His patients had no explicit recall after operation of intraoperative events, but showed evidence of implicit recall under hypnosis. Since then, many studies have been performed on patients under general anaesthesia to identify explicit and implicit recall of auditory material presented during anaesthesia, but the results have been conflicting.

In a controlled study, Bonke and colleagues [24] presented anaesthetized patients with auditory information containing suggestions concerning improved postoperative recovery and early hospital discharge. The results showed a significant benefit in the test, but not the control group. Similar studies showed reduced analgesic requirements, early discharge or both, in the test group [25, 26]. However, in a later study [27] Bonke's group failed to find any significant changes with peroperative suggestions, and Woo, Seltzer and Marr [28] found no benefit with regard to early discharge or reduced analgesic requirements, although this last study has been criticized on methodological grounds. On the whole, the results of these studies do provide some evidence of implicit (but not explicit) memory of events occurring during anaesthesia.

Other studies have looked at changes in postoperative behaviour following intraoperative suggestions. In a study by Bennett, Davies and

Giannini [29], patients were instructed to touch their ears when they heard the experimenter's voice after operation, and Goldman, Shah and Hebden [30] studied postoperative chin touching. Although patients in both these studies showed evidence of behavioural effects of intra-anaesthetic suggestion, both studies have been criticized [31–33], and Eich, Reeves and Katz [34] and Jansen and Bonke [35] found no effect of intraoperative instructions on postoperative behaviour.

Finally, tests have been devised to detect implicit memory for information presented during anaesthesia, based on a priming effect with which word lists rather than messages are presented to anaesthetized patients who are tested after operation [36]. Humphreys, Millar and Asbury [37] showed significant priming effects under anaesthesia, and Goldman [38] showed implicit memory using question and answers similar to those in "Trivial Pursuit" and found that those exposed to the answers during anaesthesia performed better. Millar and Watkinson [39] and Bonke [1990, personal communication] also showed, in word recognition tests, significant differences between experimental and control groups, with no conscious recall of hearing words presented under anaesthesia.

The majority of these studies, although indicating that implicit memory for anaesthetic events does exist, have several problems in that neither the anaesthetic techniques and drugs nor the tests used to assess recall are standardized throughout, and not all experiments attempt to ascertain the depth of anaesthesia at the time of presentation of information.

The evidence discussed so far suggests that anaesthetics affect predominantly short term or working memory, although transfer into a recall from long term memory may also be impaired.

Returning to the concept of a continuous spectrum of anaesthesia with three definable stages, it can be seen that the first stage corresponds to normal consciousness and occurs when there is failure to anaesthetize. The incidence of this anaesthetic complication is unknown. We speculate that it may be of the order of 100 cases per annum in the U.K. The second stage of awareness may be very common. In one series, 44% of patients were in this stage while undergoing surgery [4], responding to verbal commands using movement of an isolated limb, but were totally amnesic afterwards. The third stage would be described normally as adequate general anaesthesia. It is evident from the above discussion that there may be subconscious perception of events occurring during anaesthesia which may be elicited by specific tests for implicit memory or which may influence postoperative behaviour. There may be harmful effects if unguarded comments about a patient's prognosis are overheard during anaesthesia.

Studies have shown that autonomic signs as a guide to sufficient depth of anaesthesia are unreliable [4]. The isolated forearm technique also has not enjoyed widespread application, and it has not been found by everyone to be a reliable indicator of light anaesthesia [40, 41].

To eliminate the distressing occurrence of Stage I awareness under anaesthesia, some other means of determining anaesthetic depth is required. This should be not only reliable, but also predictive of light anaesthesia. Using the auditory evoked response (AER), Thornton and Newton [42] showed that the early cortical waves of the AER reflected anaesthetic concentration with all anaesthetics studied. Surgical stimulation could arouse a patient from Stage III to Stage II and increasing the dose of anaesthetic would reverse this. There was a correlation between the latency of early cortical waves in the AER and conscious awareness in five of seven subjects. The AER, therefore, may be a promising indicator of depth of anaesthesia, although further research is needed.

The facts that, under the influence of anaesthetic drugs, the brain is capable of limited processing of information and implicit memory function is likely, are of considerable interest for both anaesthetists and psychologists. For psychologists it offers more insight into the highly complex workings of the brain, and for anaesthetists it provides an opportunity to influence a patient's postoperative course.

D. Griffiths and J. G. Jones

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EDITORIAL II

OMEPRAZOLE — A USEFUL NEW AGENT?

Omeprazole is a substituted benzimidazole derivative which inhibits gastric acid production by a unique mechanism of action. Its effect on volume and pH of gastric aspirate in patients undergoing elective Caesarean section is described in this issue of *British Journal of Anaesthesia* [1].

The gastric parietal cell is stimulated to produce hydrochloric acid by an increase in intracellular cyclic adenosine monophosphate (cAMP), calcium ions, or both [2]. Acetylcholine, histamine and gastrin are mediators of acid production; this is the rationale for the use of anticholinergics, histamine type 2 (H_2) receptor blockers and surgical removal of gastrin-secreting tumours for prevention of gastric acid production. Acetylcholine, histamine and gastrin increase intracellular calcium ion concentration, but intracellular cAMP is increased only by histamine [2]. The interaction of these mediators is complex; for example, both gastrin and acetylcholine probably release histamine locally, and drugs act at different sites depending on the type of agent used.

The end point of all these pathways is the gastric proton pump, the activity of which depends on the catalyst, gastric hydrogen potassium adenosine triphosphatase (ATPase) [3]. Omeprazole inhibits this enzyme and, therefore, should result in reliable inhibition of gastric acid secretion independent of the nature of the stimulus.

Omeprazole is a weak base (pK_a 4) and is inactivated rapidly in acid environments [4]. However, satisfactory oral bioavailability has been achieved with a buffered solution and an enteric-coated gelatin formulation. Peak plasma concentrations are achieved within 30 min with the buffered solution, but are considerably slower with gelatin capsules (3–4 h) [5]. Oral bioavailability increases as gastric production is inhibited.

Omeprazole is a pro-drug which is activated in the acid-containing parietal cell canaliculi, probably by protonation [6]. It is likely that the active metabolite binds irreversibly to gastric hydrogen potassium ATPase, which explains the prolonged action of a single dose of omeprazole despite its short half-life (0.3–2.5 h) [5]. Three inactive metabolites have been identified also [4].

Omeprazole has been shown to be extremely effective in the treatment of peptic ulceration [7, 8], reflux oesophagitis [9] and, in particular, the Zollinger–Ellison syndrome [10]. However, what is its role in anaesthetic practice and what advantages is it likely to possess in comparison with cimetidine or ranitidine?

The paper by Gin and colleagues, published in this issue [1], is one of few studies to date in the anaesthetic literature. These workers found in 30 patients that omeprazole 40 mg, given orally the night before and again the morning before elective Caesarean section, was effective in reducing gastric acid volume and acidity. This is in contrast with a study published previously, which demonstrated that a single 80-mg dose of omeprazole, given orally the night before surgery, was not effective in a significant proportion of patients [11]. Direct comparisons of the effects of orally administered cimetidine or ranitidine with those of omeprazole are awaited.

A theoretical advantage of omeprazole is that the timing of i.v. administration may be less critical than other agents because of its relatively prolonged duration of action. The use of i.v. omeprazole before operation has been described recently in this journal [12]. In a double-blind, placebo-controlled study, omeprazole 40 mg was given 1 h or 3 h before surgery. The effects on gastric aspirate were similar to the findings of previous studies with i.v. ranitidine in the group given omeprazole 1 h before surgery. However, results after omeprazole given 3 h before surgery were disappointing. For example, 15 of 29 patients had gastric aspirates with pH < 2.5.

Cimetidine is associated with many significant drug interactions and increases the plasma concentration of many drugs. It inhibits metabolism of some drugs (e.g. theophylline, tolbutamide, ibuprofen, carbamazepine, mexiletine and warfarin) by binding to the haem portion of cytochrome P450; interferes with active renal tubular secretion (e.g. procainamide, triamterene and metformin); and reduces the volume of distribution of several drugs (e.g. labetalol, lignocaine, imipramine and pethidine) [13]. Ranitidine binds to cytochrome P450 also, but with fewer effects than cimetidine [14]. Several drugs which interact with cimetidine have been shown to be unaffected by ranitidine—for example propranolol, lignocaine, phenytoin and diazepam, but significant interactions have been demonstrated with others (midazolam, procainamide, warfarin, nifedipine and theophylline) [14]. Unfortunately, omeprazole has been shown to inhibit cytochrome P450 enzymes also [3]. Reduced metabolism of diazepam, phenytoin, aminopyrine and R-warfarin, but not propranolol and S-warfarin, have been reported [3, 5]. The full extent of interaction of omeprazole with other drugs remains to be demonstrated.

Very few side effects have been reported so far with omeprazole. The incidence and nature of side effects were similar to those associated with ranitidine and cimetidine in a relatively small number of patients [15]. The long term safety of omeprazole has been the subject of considerable discussion, as high doses were associated with G-cell hypertrophy and long term achlorhydria in rats with induced carcinoid tumours [16]. As yet, no similar adverse effects have been demonstrated in man. Clearly, the side effect profile of omeprazole may not be established until it has been subjected to widespread clinical use.

Omeprazole is likely to inhibit gastric acid secretion effectively in patients who are critically ill and susceptible to acute gastric erosions. However, work on this is awaited, and drug interactions may be a problem.

Type 2 histamine receptor blockers have an established role in anaesthetic practice. Omeprazole would seem to have theoretical advantages over these agents because of its mode of action. At the time of composition of the foregoing part of this editorial, there was little published evidence to suggest that omeprazole would be more useful than ranitidine in the prevention of acid aspiration in patients before surgery. However, unknown to the editorial writer, a paper similar in nature and from the same group as that appearing in this issue, was published recently in *Anaesthesia* [17] which demonstrated that omeprazole was more effective and consistent than ranitidine at maintaining gastric pH > 3.5. Further studies are clearly required to establish a possible role for omeprazole in anaesthetic practice.

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LEVELS OF CONSCIOUSNESS IN VOLUNTEERS BREATHING SUB-MAC CONCENTRATIONS OF ISOFLURANE

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SUMMARY

Eight volunteers inhaled isoflurane in concentrations of 0.1, 0.2 and 0.4 MAC, and 100% oxygen as control in separate sessions more than 1 week apart. When the end-expiratory isoflurane concentration was stable, response to verbal commands was tested, and the subjects were read 30 words in two lists. Response to the commands was impaired at 0.1 MAC in three subjects and lost at 0.2 MAC in two subjects. No subject responded at 0.4 MAC. When the subjects were questioned 1 h after exposure, memory of response to commands was lost also at these concentrations. Frequently, those who responded to the command "open your eyes" failed to remember having done so; non-responders remembered nothing. At the time of that test, at 0.4 MAC, five of eight subjects had no eyelash reflex. Both recall and recognition of neutral words was lost at 0.2 MAC and greater, but the effect of attention was demonstrated by the memory of a "shock" word by four of eight subjects at 0.2 MAC.

KEY WORDS

Anaesthesia: depth, subanaesthetic concentration. Anaesthetics, volatile: isoflurane. Memory, recall.

As anaesthesia deepens, a patient first appears to be asleep but is easily rousable, then fails to respond to commands, and finally loses the eyelash reflex. Further deepening of the anaesthetic leads to the point at which there is no response to surgical stimulation [1, 2]. At some point along this continuum, ability to process complex commands, and memory of events and words are lost. Lightening of anaesthesia during recovery has been used [3] to determine the concentration at which patients or volunteers start to respond to commands (MAC_{awake}).

In studies on surgical patients using the isolated forearm test [4] to assess awareness, the authors [5] and others [6] have observed that, although some patients responded to the test, none had recall after the anaesthetic. It may be that either premedication or the subsequent administration of greater anaesthetic concentrations during surgery contributed to this amnesia. To overcome this, it is necessary to equilibrate the same subjects for sustained periods at several concentrations on separate occasions in order to make within-subject comparisons. However, we are unaware of any study since that of Artusio with diethyl ether [7], which has attempted to quantify the loss of the various indices of consciousness in the range of alveolar concentrations of anaesthetics which bridge the gap between consciousness and a state of unresponsiveness to (unpainful) stimuli, with total loss of recall. Therefore, we have studied volunteers who were tested for memory and awareness at each of four sub-MAC concentrations of isoflurane, held stable throughout the study. No other drugs were used, to eliminate the effect of premedication and either preceding or subsequent anaesthetic concentrations.

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SUBJECTS AND METHODS

We studied eight healthy male volunteers (aged 25–43 yr). All were medically qualified and practising anaesthesia. In this way, informed consent to the administration of repeated anaesthetics could be assured. The study was approved by the hospital Medical Ethics Committee.

Each subject received, at sessions separated by at least 7 days, either 100% oxygen, or 0.1, 0.2 or 0.4 MAC isoflurane (end-tidal) in oxygen; 1.0 MAC = 1.15% [8]. No correction was made for the age of the subjects. The end-tidal concentrations were maintained by the technique of overpressure. The inspired concentration of isoflurane was adjusted manually, using a mass spectrometer as a guide, to hold the end-expiratory concentration at target value.

The test sessions were divided into six periods, the first breathing 100% oxygen via a pilot's face mask, and subsequent periods breathing the test mixture with the subjects unstimulated, given commands, given word lists, and again unstimulated, respectively, with the subject breathing 100% oxygen in the final period (table I).

Gas measurements were made using a quadrupole medical mass spectrometer calibrated against standard gas mixtures before and after each experiment. End-tidal concentrations of carbon dioxide and isoflurane were recorded continuously and displayed, and oxygen and nitrogen concentrations monitored in order to detect leaks from the face mask. A short length of plastic tubing was added to extend the heated sample tube of the mass spectrometer, and the gas sampled 1 cm inside the nasal cavity. The subjects were requested to keep the mouth closed throughout the study and were, if necessary, assisted by support of the jaw.

Experiments were conducted in a quiet darkened room, with the subject placed on a hospital (tilting) bed. On all occasions, the subjects were prepared as if for day surgery. They came starved and unpremedicated, and a 22-gauge cannula was inserted for venous access. Arterial pressure and heart rate were recorded automatically every 1.5 min and the electrocardiogram was monitored continuously. The room was fully equipped for general anaesthesia including drugs, facilities for tracheal intubation and suction apparatus. An independent anaesthetist supervised the subject, and assessed clinically the depth of anaesthesia, supporting the airway when appropriate.

TABLE I. *Experimental programme*

Period	Activity	Duration (min)
1	Breathing 100% oxygen	10
2	Test gas: unstimulated then clinical assessment of depth	10
3	Test gas: given commands	2.75
4	Test gas: hears words	2.75
5	Test gas: unstimulated	5 5
6	Breathing 100% oxygen	Until awake

Psychological tests were of three types. The level of consciousness was assessed at the end of the second period when the end-tidal concentration of isoflurane had been stable for at least 10 min (table I). The subject was asked loudly to open his eyes and close them. If there was no response, or after the response, the eyelash reflex was tested. In the third period, two sets of 20 commands were presented. In the first set it was explained that, for example, blue represented left, and red right, and the subject should raise the appropriate index finger in response to the colour (the commands were simply "blue" or "red"). Both the existence and the correctness of a response were scored. In the second set the same commands were given, without the colour code, but merely the words "left" and "right".

During the fourth period the subject heard two lists of 15 words. He was instructed to memorize all the words, and in which list they were presented. He was asked also to signal, by raising a finger, that he had heard each word. Included in each word list was a "shock" word (usually amusing); any additional response of the subject was noted.

One hour after the experiment the subject was interviewed, always by the same investigator. On each occasion, the subject was asked to describe, in his own words, what he could remember, and then specifically if he could remember the "open eyes" command, the finger raising tests, and hearing and responding to the words. He was then asked which words he remembered spontaneously and from which list. A list of 30 words was read out containing some of the test words, some synonyms and some homonyms, and the subject was invited to indicate if the word had been presented and, if so, in which list.

The experiments were constructed to allow

TABLE II. *The 2 × 2 contingency table used in the calculation of the discrimination index for recognition tasks (see text)*

Response	Presented	
	Old words	New words
Recognized	Correct (*a*)	Incorrect (*b*)
Not recognized	Incorrect (*c*)	Correct (*d*)

blinding of both subject and testers. Specifically, only the vaporizer operator knew which concentration of isoflurane was being administered and, when 100% oxygen was used, small amounts of isoflurane ($< 0.05\%$ inspired) were added to the circuit at the start of the test to blind the subject. The tests and words had been pre-recorded on tape cassette. There were four sets of commands and words. Each subject received all four sets during the study, and the order of administration of the four concentrations and the four sets of commands was arranged randomly according to a replicated graeco–latin square. Statistical analysis was performed using Friedman's ANOVA to compare treatments, and Cochran's Q test to compare proportions. Analysis of variance was performed on the discrimination index (see below) to investigate differences between treatments, subjects, days and the recognition of words and lists. A discrimination index was used to assess recall after hearing a list of words during the anaesthetic. The subjects were presented subsequently with two types of word: those present in the original list and new words. To recognize a word, the subject had to discriminate between the old and new words. This task generates a 2 × 2 contingency table (table II).

There are two types of correct response: recognizing old words, and not recognizing new words. Luce and Galanter [9] suggested the following formula: $(ab/cd)^{\frac{1}{2}}$ (see table II). Using this formula, an infinite number of chance responses would be 1.0, a response less than chance gives values in the range 0–1, and a response more than chance, values from 1 to infinity. Problems which would have arisen if a, b, c or d were zero were avoided by adding 1/6 to each of the four cells (Tukey's version of Yates' correction). In this study $\log_e$ were taken to make the distribution symmetrical. In the results (table VII) the effect of taking $\log_e$ would imply that recognition worse than chance has therefore a negative value, chance recognition is zero (i.e. $\log_e 1 = 0$), and recognition better than chance is greater than zero.

RESULTS

In all subjects, the range of concentrations used spanned the transition from awake to unconscious (defined as loss of response and recall). All reported a sudden loss of consciousness and an equally sudden awaking, always within 5 min of the end of period 5.

Level of consciousness (tested by the command "open your eyes", and eyelash reflex). At 0.4 MAC all the subjects failed to respond to the command, and five had an absent eyelash reflex; seven were obviously asleep, snoring or requiring airway support, and the eighth was making unco-ordinated movements reminiscent of stage two excitation. Seven of eight subjects opened the eyes on command at 0.2 MAC, and the eyelash reflex was present in all (table III). There were highly significant differences between the four treatments (Friedman's ANOVA, $P = 0.004$).

Memory of the test. Table III shows the relationship between the memory of being asked to open eyes and the concentration of isoflurane administered. There were highly significant differences between treatments (Cochran's Q test, $P < 0.001$). The test demonstrates that, even at the least concentration, some of the subjects showed impairment of recall while they appeared to react normally. Absence of response to command guaranteed no recall, whereas response to command was not necessarily remembered.

TABLE III. *Memory of assessment of consciousness (response to the command: "open your eyes") in eight subjects tested at four concentrations of isoflurane. This should be compared with the actual compliance, and the level of consciousness as assessed by the eyelash reflex*

	MAC isoflurane			
	None	0.1	0.2	0.4
Memory of assessment of consciousness				
No	0	2	6	8
Yes	8	6	2	0
Compliance with the command "open your eyes"				
No	0	0	1	8
Yes	8	8	7	0
Eyelash reflex				
Absent	0	0	0	5
Present	8	8	8	3

TABLE IV. *Response to commands (finger raising) in eight subjects at four concentrations of isoflurane*

Score (out of 40)	MAC isoflurane 0	0.1	0.2	0.4
0	0	0	2	8
23	0	0	1	0
24	0	0	1	0
28	0	0	1	0
32	0	0	1	0
37	0	0	1	0
38	0	0	1	0
39	0	3	0	0
40	8	5	0	0

TABLE V. *Finger raising on hearing each word from a list of 30 words. Eight subjects were tested at each of the four concentrations of isoflurane*

Score (out of 30)	MAC isoflurane 0	0.1	0.2	0.4
0	0	0	3	8
18	0	0	1	0
24	0	1	1	0
25	0	1	0	0
30	8	6	2	0

Finger raising. There were no significant differences between the responses to the coded and uncoded commands (pooled results in table IV). The differences between treatments were highly significant (Friedman's ANOVA, $P < 0.001$). There was impairment of response in some subjects at 0.1 MAC, and in all at 0.2 MAC. At that concentration subjects either responded to more than 50% of the commands ($n = 6$) or not at all ($n = 2$). No responses were seen at 0.4 MAC. All the subjects who responded to the commands remembered hearing them 1 h later, and none of the non-responders remembered.

Word lists. Similar responses were observed when the subjects were asked to finger raise when they heard each of the 30 words (table V) and, again, total failure to respond coincided with lack of memory of the events.

Table VI shows various aspects of memory for words. Recall of word lists was measured in terms of the proportion of words correctly recalled. The cognition task was analysed using a discrimination index [9]. Three types of discrimination are shown in the table: between words presented and words not presented; between words in list 1 and words not in list 1; between words with meanings that were presented, and those with meanings not presented. Finally, recall of shock words is given in terms of the number of subjects who recalled them. With the exception of the shock word, the results are the same for each measure. There was a highly significant effect of anaesthetic concentration such that at 0 and 0.1 MAC, memory was good, while for 0.2 and 0.4 MAC, performance was no better than chance.

There was no evidence of an intermediate state of consciousness in which some but not all aspects

TABLE VI. *Effect of isoflurane concentration on eight subjects in four separate sessions on recall and recognition of words 1 h after exposure. There is an abrupt change in performance between 0.1 and 0.2 MAC for all aspects except the "shock" word, which was remembered for half the subjects at 0.2 MAC. The discrimination index (better than chance, > 0; chance = 0; worse than chance, negative values) is described in the text.* SEM *derived from analysis of variance;* P *value from comparison of all four concentrations*

	MAC isoflurane					
	0	0.1	0.2	0.4	SEM	*P*
Recall (Median of proportion of words correctly recalled)	0.71	1.0	0.0	0.0		< 0.001
Range	0.17–1.0	0.0–1.0	0.0–0.5	0.0–0.0		
Word recognition (discrimination index)	1.82	1.13	0.36	0.14	0.22	< 0.001
List recognition (discrimination index)	1.83	1.73	−0.76	−0.21	0.51	0.004
Meaning recognition (discrimination index)	1.55	0.84	0.19	0.1	0.25	0.003
Memory of shock words (No. of subjects remembering)	8/8	6/8	4/8	0/8		< 0.001

TABLE VII. *Summary of findings. The effect of increasing MAC on response to commands, recall of those commands, memory of words, and clinical anaesthetic depth*

MAC	Effect
0	Full response and recall
0.1	Response full; recall impaired
0.2	Response impaired; recall and recognition of words and events lost. Memory of "shock" words still present
0 4	Loss of response; loss of recall and recognition; loss of eyelash reflex in 62% of subjects

of a word could be recalled. The results of memory for words closely parallels the results of the other assessments.

General observations. None of the subjects experienced any discomfort during the experiments. It was interesting to note that hunger, rather than nausea, followed the administration of isoflurane alone, even at the greater concentrations. End-tidal concentrations of carbon dioxide remained within 10% of their initial values at all concentrations of isoflurane, but there was a clearly discernible upward drift in sleeping subjects, reversed by arousal. Satisfactory end-tidal plateaux on the isoflurane registration were seen when using nasal sampling. Mouth breathing and system leaks were detected rapidly and corrected. No clinically significant changes (> 10%) occurred in either heart rate or arterial pressure.

DISCUSSION

This study has established the end-tidal concentrations of isoflurane in oxygen at which consciousness is lost in unpremedicated subjects. There is a distinction between the loss of eyelash reflex (five of eight) at 0.4 MAC, loss of response to simple commands between 0.2 MAC and 0.4 MAC, and loss of memory of these commands at the same MAC fraction. Memory of specific words from a bland list was lost at 0.2 MAC (four subjects remembered "shock" words at this concentration). Memory of the specific tasks was related closely to the performance of those tasks. On no occasion, however, did any subject remember events when he did not respond, although the converse was sometimes true for the simple task of opening eyes. The findings are summarized in table VII.

$\text{MAC}_{\text{awake}}$, the mean concentration of an anaesthetic agent at which a patient awakes from anaesthesia, has been established by identifying the alveolar concentration at which the patient responds to command at the end of general anaesthesia [1]. In those studies, the lag between alveolar concentration and brain concentration was overcome by testing after the end-tidal concentration had been maintained for 15 min. In the present study, testing for wakefulness was conducted also in the middle of a protracted period of constant end-tidal concentration, and for each subject, only one concentration was used in each session. Thus we are confident in the assumption that brain equilibration at the chosen concentration had taken place.

The aim of this study was to establish the alveolar concentration of isoflurane producing unconsciousness in the absence of pain stimulation. The definition of unconsciousness, or the absence of awareness, has been examined [10, 11], and in particular the lightest levels have been classified for ether anaesthesia by Artusio [7]. Similar stages in the lightest levels of isoflurane sedation have been identified in this study, although without testing for analgesia. This has been done in relation to the types of testing and their results. The simplest test, asking the subject to open his eyes, and then testing for the eyelash reflex, reflects routine anaesthetic practice. The results show that these tests are, in the unparalysed patient, evidence of adequate hypnosis. The finger raising tasks were designed to identify intermediate levels of impairment of performance. Although the response required in both the simple and coded tests is identical, the coded task is more difficult, as greater demands are placed upon the cognitive system. The subject has to remember the arbitrary code, and use it to translate command into response. In contrast, the second task, direct command, can be accomplished largely by automatic response. Impairment to the coded task would have been expected at a lower anaesthetic concentration. This was not the case, and it would appear that isoflurane produces a sharper "cut-off" in these tests than had been found with some benzodiazepines [12].

In order that an event may be remembered, it must be processed by the central nervous system. In general, the more thorough the processing, the better remembered is the event [13]. Memory for words has been studied widely from this point of view, and it has been shown that memory impairment caused by sedative drugs may be attributed to a reduction in the extent to which the words are processed [14]. In the paradigm used in this study, three aspects of the words presented were considered: to which list the word belonged, what the word resembled, and what the word meant. When processing is complete, all these aspects of the words are remembered. With inadequate processing as a result of sedation, the subjects may no longer remember to which list the word belonged or what it resembled, but they remember what it meant. They would thus identify synonyms, incorrectly. It was expected that, at intermediate concentrations of anaesthetic, subjects would have remembered words, but not to which list they belonged. Likewise, it would be expected that spontaneous recall was impaired more than recognition of the same word, synonyms or homonyms. In this study, no such gradation could be detected.

The finding of minimal impairment of response to commands at the least concentration (0.1 MAC), is similar to that found with 0.1 MAC halothane [15]. The memory of hearing those commands was unimpaired. The effect of arousal to attention is demonstrated well by the consistent memory of the shock words, even for some subjects at 0.2 MAC. At a greater concentration of anaesthetic, memory of events becomes impaired, while responses may be retained. This is illustrated best in table III, and agrees with our own previous findings [4], when the isolated arm technique was used to demonstrate awareness during anaesthesia in patients not undergoing surgery, and none of the responding patients remembered having responded. Similarly, Russell [6] found that surgical patients who responded in the isolated arm test rarely remembered it. We found that responses were lost at an anaesthetic concentration between 0.2 and 0.4 MAC. The greatest concentration used (0.4 MAC) resulted in the onset of true unconsciousness, with loss of response to verbal command, and in five of eight subjects, eyelash reflex.

Simple observation of the subjects was, at the intermediate concentrations, unhelpful. Many appeared to be asleep, but were easily rousable on command. At a concentration between 0.2 and 0.4 MAC isoflurane this rousability was lost, and this would seem to determine the transition between sleep and light anaesthesia. In this study no painful stimulus was used, and it is not possible to say if this concentration could prevent arousal to wakefulness (i.e. responding and recalling) by surgical stimulation or tracheal intubation. Previous studies defining the MAC fraction inhibiting response to tracheal intubation [16], and MAC [2] itself are of no help in assessing arousal by stimulus because, in those studies, any movement meaningful or otherwise was used as an endpoint, and such a movement does not necessarily indicate cerebral activity. This aspect requires further study: every anaesthetist has seen some response to strong stimuli in the unparalysed patient, but it has yet to be established if, when the level of sedation achieved in this study at 0.4 MAC has been reached, a patient can be stimulated to wakefulness.

Evidence from a previous study [17] and that of McMenemin and Parbrook [18] suggests that, at low concentrations, isoflurane may have a particularly powerful hypnotic effect compared with nitrous oxide. Isoflurane has not been compared with other volatile agents, but this property may explain the difference between our results and those obtained in the $\mathrm{MAC}_{\mathrm{awake}}$ study for other volatile agents which suggest a value of 0.6 MAC [1].

All the subjects found inhaling isoflurane acceptable or pleasant, and suffered no nausea. We would therefore suggest that isoflurane alone should be investigated further as a suitable agent for producing sedation during local analgesia, as it has already been shown by Kong, Willatts and Prys-Roberts [19] that low concentrations are suitable for sedation in intensive care patients.

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EFFECT OF ORAL OMEPRAZOLE ON INTRAGASTRIC pH AND VOLUME IN WOMEN UNDERGOING ELECTIVE CAESAREAN SECTION

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SUMMARY

We have studied in obstetric patients the efficacy of omeprazole in increasing intragastric pH to more than 2.5 and reducing volume to less than 25 ml. Omeprazole 40 mg was given orally the night before and again on the morning of surgery to 30 Asian women scheduled to undergo elective Caesarean section. After induction of anaesthesia, a gastric tube was inserted and intragastric contents aspirated. Volume and pH were recorded and measurements were repeated on completion of surgery. The median (range) volume was 2 (1–13) ml before surgery and 4 (0–14) ml at the end of surgery. There was insufficient volume to measure pH in all patients. The median (range) pH was 6.7 (4.6–7.4) before surgery in 20 patients and 6.6 (4.6–7.8) at the end of surgery in 28 patients. No adverse drug reactions were noted in mothers or neonates. Omeprazole 40 mg orally twice before elective Caesarean section appeared to be effective in reducing intragastric volume and acidity to acceptable values.

KEY WORDS

Anaesthesia: obstetric. Gastrointestinal tract: intragastric pH, omeprazole. Premedication: omeprazole.

Pulmonary aspiration of acidic gastric contents remains an important contributor to obstetric mortality [1]. In patients requiring general anaesthesia, prophylaxis includes reduction of intragastric volume and acidity with various combinations of histamine type 2 (H_2) receptor antagonists, antacids and metoclopramide. No ideal therapy has been defined and many different regimens are followed [2]. An intragastric pH less than 2.5 and volume greater than 0.4 ml kg^{-1} (approximately 25 ml) have been suggested as being particularly dangerous [3], although this has been questioned [4]. Studies of pulmonary aspiration in rats have shown that pH is a more important factor than volume in determining lung injury [5] and mortality [6].

Omeprazole is a specific inhibitor of the enzyme H^+K^+ATPase, which acts at the final step in the acid secreting pathway and is found only in the parietal cell [7]. Suppression of gastric acid secretion is more prolonged by omeprazole than by H_2 receptor antagonists, without an increase in side effects. Omeprazole is effective in treatment of acid-related gastrointestinal diseases [7]. Omeprazole was suggested for obstetric anaesthesia many years ago [8], but a single 80-mg dose the night before surgery was associated with an intragastric pH < 2.5 in three of 20 obstetric patients [9]. Repeated administration of omeprazole has a cumulative effect on acid inhibition [7] and should be more effective in increasing intragastric pH than a single dose.

We undertook a non-comparative study to assess the efficacy of two doses of omeprazole 40 mg in reducing gastric acidity and volume in women undergoing elective Caesarean section.

PATIENTS AND METHODS

The study was approved by the Research Ethics Committee of the Chinese University Faculty of

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This article is accompanied by Editorial II.

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Medicine. Written informed consent was obtained from all patients.

We studied healthy Asian women with uncomplicated pregnancies of at least 36 weeks duration undergoing elective Caesarean section before midday. Patients were excluded if they had symptoms of acid-related gastrointestinal disease, previous gastric surgery, known drug allergy or abuse, or ingestion within the past 4 days of drugs known to affect gastric motility and secretion. Laboratory investigations included routine haematological, biochemical and liver function tests.

Omeprazole was provided as enteric coated granules in hard gelatin capsules, each containing 20 mg. Omeprazole 40 mg, with 50 ml water, was given orally at 20:00 the night before surgery and again at 06:00 on the morning of surgery. Patients were fasted from midnight.

All women were transported to the operating theatre in the lateral position. Before induction of anaesthesia patients were questioned directly for unusual symptoms which might indicate adverse drug reactions with omeprazole. Patients were maintained in the left lateral tilt position and monitored with the electrocardiograph and an automated non-invasive arterial pressure device.

After preoxygenation for at least 3 min, rapid sequence induction of anaesthesia was performed with thiopentone 4 mg kg^{-1} while cricoid pressure was applied. Suxamethonium 1.5 mg kg^{-1} was given i.v. to facilitate tracheal intubation and neuromuscular block maintained with atracurium 0.5 mg kg^{-1}. Ventilation of the lungs was controlled to maintain an end-tidal carbon dioxide concentration of 4.0–4.5 %. Anaesthesia was maintained with 50 % nitrous oxide and 1 % enflurane in oxygen until delivery, after which nitrous oxide was increased to 70 % and enflurane decreased to 0.5 %. At delivery, oxytocin 10 u. and morphine 0.2 mg kg^{-1} were given i.v. Enflurane was discontinued at commencement of skin closure and 100 % oxygen administered at the end of surgery. Atropine 1.2 mg and neostigmine 2.5 mg were given to all patients to antagonize residual neuromuscular block.

Intragastric pH and volume were measured after induction of anaesthesia and again on completion of surgery. A 16-French gauge Salem Sump tube was inserted orally and correct position in the stomach checked by auscultation of injected air. We attempted to maximize returned volume by repeated aspiration with the tube rotated and withdrawn 10 cm and readvanced. The volume of aspirate was recorded and pH measured within 1 h with a Corning 240 pH meter calibrated daily at pH 4, 7 and 10.

At delivery, samples of maternal venous (MV), umbilical arterial (UA) and umbilical venous (UV) blood were obtained in most patients. Plasma was separated and stored at −20 °C for subsequent assay for omeprazole.

Plasma analysis for omeprazole was performed by the Department of Bioanalytical Chemistry, AB Hässle, Sweden. The method used high pressure liquid chromatography on a silica gel with mobile phase of methylenehydroxide in methanol. The flow rate was 1.5 ml min^{-1} and the eluent was monitored by u.v. detection at 302 nm. The minimum determinable concentration of omeprazole was 20 nmol $litre^{-1}$ in plasma and the relative SD was 10–15 %.

Neonatal Apgar scores at 1 and 5 min were recorded. Weight gain and suckling ability were reviewed daily until discharge.

Patients were questioned again after operation for unusual symptoms and the preoperative laboratory investigations were repeated before discharge.

Simple linear regression was used to evaluate associations among pH and volume data, omeprazole concentrations and the time from the last dose of omeprazole. The Wilcoxon rank sum test was used to compare UA with UV concentrations of omeprazole and the initial with the final aspirate pH and volume data. $P < 0.05$ was considered significant.

RESULTS

Although 33 women were entered into the trial, three were withdrawn. One patient required emergency Caesarean section and surgery was deferred in the other two. Thirty women, aged 23–38 yr, weighing 50–81 kg and of 37–39 weeks gestation completed the study.

The duration of surgery ranged from 30 to 80 min. The time from the last dose of omeprazole to intragastric pH and volume measurements ranged from 3.0 to 6.4 h.

The median (range) gastric volume was 2 (1–13) ml before surgery and 4 (0–14) ml at the end of surgery (fig. 1). There was insufficient volume to measure intragastric pH in 10 patients before surgery and two patients at the end of surgery. The median (range) pH was 6.7 (4.6–7.4) before surgery and 6.6 (4.6–7.8) at the end of surgery.

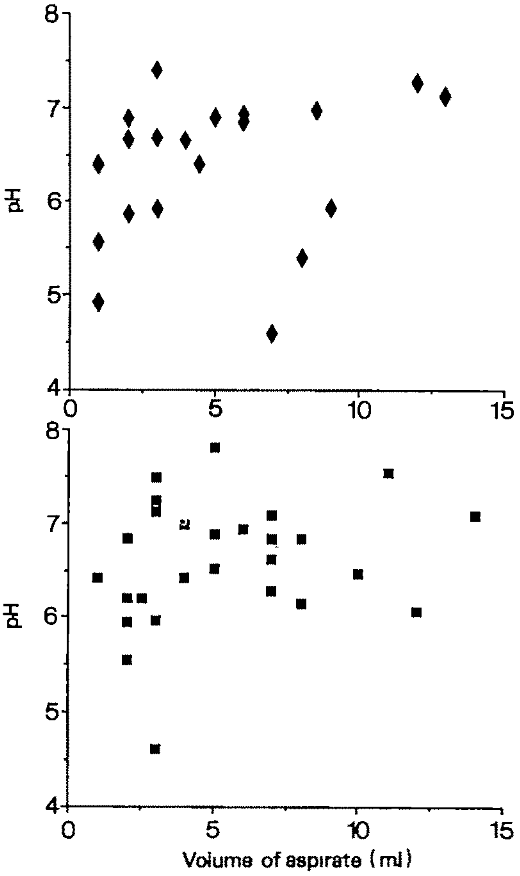

FIG. 1. Intragastric pH and volume at the start (◆) and at the end (■) of surgery.

Two pH measurements were possible in 19 patients with the final pH often slightly greater than the initial pH ($P < 0.01$). Volume and pH were not related to time since the last omeprazole dose.

Maternal and umbilical blood samples were obtained 3.0–5.5 h after the last dose of omeprazole and omeprazole was detectable in all samples (table I). UA and UV concentrations of omeprazole were similar in the same neonate and always less than the corresponding MV sample. There was good correlation between omeprazole concentrations in MV and UV ($r = 0.96$) and MV and UA ($r = 0.95$). Values were not related to gastric pH or the time after the last dose of omeprazole.

TABLE I. *Omeprazole concentration data from maternal vein (MV) (n = 25), umbilical vein (UV) (n = 29) and umbilical artery (UA) (n = 20). CI = Confidence interval*

	Mean	SD	Range	95 % CI
MV (μmol litre^{-1})	1.64	1.12	0.37–4.83	
UV (μmol litre^{-1})	0.88	0.52	0.17–2.00	
UA (μmol litre^{-1})	0.94	0.49	0.20–1.95	
UV/MV ($n = 25$)	0.54	0.10	0.31–0.71	0.49–0.58
UA/UV ($n = 20$)	1.02	0.16	0.81–1.58	0.95–1.10

Apgar scores were satisfactory. Two neonates were admitted to the intensive care unit. One neonate was of low birth weight (2.2 kg) and developed a respiratory infection, while the other was admitted on the 3rd day for phototherapy of physiological jaundice. All neonates had satisfactory weight gain and suckling ability, except for the low birth weight neonate in intensive care.

No adverse symptoms were elicited from the mothers and the postoperative laboratory investigations showed no abnormal variation from preoperative values.

DISCUSSION

Omeprazole 40 mg orally the night before and again on the morning of surgery appeared to be effective in increasing gastric pH to more than 2.5 while keeping intragastric volume less than 25 ml.

The technique of blind gastric aspiration underestimates intragastric volume [10], but it is a simple method which has been used commonly in similar trials. Dye dilution measurement of gastric volume may not be superior in anaesthetized patients [11] and extra complexity is added to the procedure. Even if one considers that the postoperative aspirate may have been present at the beginning of surgery, the addition of the two volumes was still low (range 2–20 ml). Omeprazole has been found to reduce the volume of gastric juice secretion [12].

The pH of gastric aspirate may be more important than volume in determining pulmonary damage [5, 6]. Although pH was not measurable in 10 patients initially, subsequent pH measurements at the end of surgery were obtained in nine and all were satisfactory.

Our results are better than the previous study of a single 80-mg dose in obstetric patients in which six of 20 patients failed either volume or pH criteria [9]. This is probably because of the additive effect of the two omeprazole doses on acid inhibition, although patient and procedural differences cannot be discounted. The time from drug administration to induction of anaesthesia was shorter in our study than the 11.8–16.3 h investigated previously [9].

The safety of all new drugs in obstetric anaesthetic practice must be considered. Omeprazole is a pro-drug which is activated only at pH less than 4. It has no effect on other H^+ secreting cells in the body. After activation, the specific target of the drug is the enzyme H^+K^+ATPase, causing a non-competitive, long lasting inhibition of hydrochloric acid secretion. Omeprazole is eliminated rapidly, with an elimination half-life of 0.5–1.5 h, but the effect on acid secretion does not correlate with plasma concentrations [7]. Omeprazole is metabolized in the liver via the cytochrome P450 system and therefore alterations in disposition of other drugs metabolized through that system can be surmised. Omeprazole has been shown in healthy subjects to decrease the clearance of phenytoin and diazepam [7].

Placental transfer of omeprazole has been measured in sheep [13] and humans [9]. In the latter study, neonatal intragastric pH was almost neutral after delivery, but subsequent changes in acidity were not evaluated. However, the normal neonatal intragastric pH at birth is almost neutral [14] and omeprazole would not be activated in these conditions. The umbilical concentrations of omeprazole in our study were greater than those reported previously [9] because of the shorter dose to sampling interval. There are no data on the neonatal metabolism of omeprazole.

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DICLOFENAC FOR DAY-CARE ARTHROSCOPY SURGERY: COMPARISON WITH A STANDARD OPIOID THERAPY

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SUMMARY

Sixty unpremedicated patients presenting for day-care arthroscopy surgery were allocated randomly to receive diclofenac 1 mg kg^{-1} i.m., fentanyl 1 µg kg^{-1} i.v. or no analgesic during the course of anaesthesia. Patients receiving fentanyl had slightly, although not significantly prolonged recovery times. Patients receiving diclofenac had significantly improved postoperative visual analogue pain scores compared with patients receiving placebo medication ($P < 0.05$*). With fentanyl, pain scores were reduced also, but the effect was not statistically significant. Both fentanyl and diclofenac produced significant reduction in postoperative analgesic requirements (*$P < 0.05$*). We conclude that diclofenac 1 mg kg^{-1} i.m. was an effective analgesic for arthroscopic procedures on the knee and is a useful alternative to opioids for day-care patients.*

KEY WORDS

Analgesics: diclofenac, fentanyl. Pain postoperative. Surgery arthroscopy, day-care.

In recent years the practice of day-care anaesthesia for minor surgery has increased markedly, with resulting improved efficiency and undoubted patient preference [1]. The challenge to produce a "street-fit" patient with rapid recovery from anaesthesia has fuelled a demand for shorter acting anaesthetic agents with minimal hangover effects. Despite the development of shorter acting opioid analgesic drugs, the provision of analgesia poses problems, as these drugs have long terminal elimination half-lives [2, 3] and have been associated with prolonged recovery [4–6].

Non-steroidal anti-inflammatory drugs (NSAID) have been shown to provide effective analgesia in many surgical situations, alone or as adjuncts to opioid analgesia [7–11]. They produce fewer side effects—specifically, absence of sedation or respiratory depression, and a lower incidence of nausea.

Diclofenac is a non-steroidal drug available for parenteral administration and with a low incidence of side effects [12]. It is absorbed well following i.m. injection and has a rapid onset of action combined with a prolonged duration of analgesia. The purpose of this study was to examine the efficacy of diclofenac as a sole analgesic in the context of day-care arthroscopy surgery and to compare its action with standard opioid therapy.

PATIENTS AND METHODS

Unpremedicated day-care patients (aged 16–65 yr and within 10% of their ideal weight) presenting for arthroscopic examination of the knee were considered eligible for the study. In addition to the normal exclusions for day-care surgery, patients taking NSAID, and those with a history of peptic ulceration or a known sensitivity to any of the agents used were excluded. The study was approved by the University Ethics Committee and all patients gave informed verbal consent before operation. The use of a 100-mm visual analogue pain scale as described previously [13, 14] was explained to all subjects.

On arrival in the anaesthetic room, patients were allocated randomly to receive one of the three treatment regimens:

Group 1 received diclofenac 1 mg kg^{-1} to a maximum dose of 75 mg i.m. in the vastus lateralis muscle of the contralateral limb following induction of anaesthesia and 5 min before inflation of the limb tourniquet.

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Group 2 received fentanyl 1 μg kg^{-1} to a maximum dose of 75 μg i.v. 2 min before induction of anaesthesia followed later by saline 1 ml into the same site as in group 1.

Group 3 received i.m. saline only.

Venous access was maintained using an i.v. cannula in an upper limb vein. Anaesthesia was induced using propofol 2.0–2.5 mg kg^{-1} and maintained by spontaneous ventilation via a Bain system of a mixture of 66% nitrous oxide in oxygen with isoflurane added as required. Patients were monitored throughout using an ECG and automated arterial pressure device.

After operation, patients were admitted to the recovery ward, where the following assessments were made by a trained recovery nurse unaware of the patient's therapy group: times from discontinuation of inhalation anaesthetic agents to eye opening and giving correct date of birth; an objective measure of sedation at 30 and 90 min after operation on a four-point scale: 1 = fully awake; 2 = slightly drowsy; 3 = drowsy but easily rousable; 4 = rousable only with difficulty.

In addition, pain was assessed by the patient at 30 and 90 min after operation, using a 100-mm visual analogue pain scale and supplementary oral analgesia (co-codamol) was offered routinely by the recovery ward staff, who were unaware of the patient's treatment group. Individual analgesic requirements were recorded and any adverse sequelae such as nausea or vomiting noted.

Recovery times were analysed using one-way analysis of variance. Visual analogue pain scores were compared using Kruskal–Wallis and Mann–Whitney *U* tests; analgesic requirements were analysed using two-tailed Fisher's exact probability test. $P < 0.05$ was considered significant.

RESULTS

Sixty patients were admitted to the study; five were removed subsequently because of incomplete collection of data. The groups were similar with respect to age, weight, sex distribution and numbers requiring arthroscopic meniscectomy (table I).

TABLE I. *Demographic data (mean (SD)) for patients in the three groups*

	Diclofenac ($n = 19$)	Fentanyl ($n = 18$)	Untreated ($n = 18$)
Age (yr)	30.7 (7.8)	33.6 (12 6)	29 6 (9.2)
Sex (M/F)	17/2	16/2	15/3
Weight (kg)	75.1 (8 2)	72.1 (8.8)	72.4 (14.2)
Duration of anaesthesia (min)	22.5 (13 0)	19.4 (9.9)	18.4 (8 7)
Meniscectomy (*n*)	9	9	9

Patients receiving fentanyl had slightly longer mean recovery times than both the diclofenac and untreated groups, although the differences were not significant. Recovery was generally rapid, and most patients were deemed fully awake at the 30-min assessment (table II). One patient, in the untreated group, was still slightly drowsy at the 90-min assessment.

TABLE II. *Times to eye opening (mean (SD)) and 30-min sedation scores*

	Diclofenac	Fentanyl	Untreated
Time to eye opening (min)	8.3 (5.5)	10.0 (6.2)	9 8 (5.7)
Sedation score (*n*)			
1	16	15	17
2	2	3	1

Although lower average pain scores were recorded in the diclofenac group at 30 min, they were not significantly different from the two other groups. Intergroup comparisons at the 90-min assessment show a significant improvement in pain scores in the diclofenac-treated group with respect to control. Patients in the fentanyl group also had lower pain scores than the untreated group at 90 min, but the difference did not achieve statistical significance (table III).

Whereas nine of 18 patients in the untreated group required supplementary analgesia after operation, only one of 18 and two of 19 in the fentanyl and diclofenac groups, respectively, required additional pain relief after operation. This reduction in analgesic requirement was significant ($P < 0.05$) (table IV). Four patients in the untreated group and two in the diclofenac group received supplementary analgesia before the 90-

TABLE III. *Pain scores at 30 and 90 min (mean rank [median (quartile range)]).* * $P < 0.05$ *(compared with untreated)*

	Diclofenac	Fentanyl	Untreated
30 min	24.08 [24 (36)]	30 14 [30 (31)]	30 00 [29 (25)]
90 min	20.42* [11 (24)]	27.88 [19 (27)]	32.25 [27 (26)]

TABLE IV. *Postoperative analgesic requirements in each group.* *$P < 0.05$ *within drug group*

	Diclofenac ($n = 19$)	Fentanyl ($n = 18$)	Untreated ($n = 18$)
No analgesia	17	17	9
Analgesia required	2*	1*	9

min assessment. These were not excluded from the visual analogue score analysis. There did not appear to be any increase in analgesic requirement or pain scores in those patients in whom arthroscopic meniscectomy was performed, compared with a non-operative procedure.

One patient in each of the untreated and diclofenac groups, and two in the fentanyl group, experienced nausea. No patient experienced vomiting.

DISCUSSION

The increasing popularity of day-care anaesthesia has occurred concomitantly with the development of shorter acting anaesthetic agents. There is some evidence that the requirements for day-care anaesthesia of rapid recovery and minimal side effects are not satisfied completely by the newer short acting opioid analgesic drugs. Large individual variation in sensitivity [15] led to reports of prolonged recovery and impaired psychomotor functioning [4, 16] with both fentanyl and alfentanil. There is no simple test for street fitness in day-care surgery and it is claimed that up to 30% of patients disregard medical advice and journey home unaccompanied, while 9% of car owners drive themselves home [1]. Thus it may be prudent to avoid the use of supposed short acting opioid drugs in day-care anaesthesia if satisfactory alternatives exist.

The non-steroidal anti-inflammatory drugs may perhaps be used more frequently in this setting, as they are generally devoid of significant CNS effects and have a lower incidence of nausea and vomiting than opioid drugs [17]. They are of proven benefit not only in dental [8] and orthopaedic pain [18, 19], but may alleviate severe pain following general surgery [9–11, 20].

Diclofenac offers advantages over opioids and fulfils many properties of the ideal analgesic. It is available for oral, rectal and i.m. administration and it has a rapid onset and prolonged duration of action. The drug has a high therapeutic index and plasma concentrations are affected little by age or renal or hepatic impairment [12, 21]. In normal therapeutic doses, it has minimal effects on bleeding time and is associated with a low incidence of gastrointestinal upset [12].

In this study, i.m. diclofenac was as effective as a standard dose of fentanyl given i.v. immediately before operation in alleviating postoperative pain following arthroscopic procedures. It also reduced significantly postoperative analgesic requirements. The early comparability of pain scores in the three groups at the 30-min assessment may be explained by hangover effects of the anaesthetic or, perhaps, a delay in the penetration of diclofenac into the surgical field occasioned by the use of a limb tourniquet.

We found no evidence of significant prolongation of recovery in the fentanyl-treated group. However, the assessment of times to eye opening and objective sedation scores are relatively simple tests of recovery and it is possible that more sophisticated psychomotor testing may have revealed subtle differences.

In summary, in this study, diclofenac 1 mg kg^{-1} i.m. appeared to be an effective analgesic in day-care knee arthroscopy surgery. We feel it may offer a useful alternative to opioid drugs in this and possibly other minor day procedures.

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EFFECT OF INDOMETHACIN ON PAIN RELIEF AFTER THORACOTOMY

T. PAVY, C. MEDLEY AND D. F. MURPHY

SUMMARY

The effect of indomethacin on postoperative pain was studied in 60 adult patients undergoing thoracotomy in a prospective, randomized, double-blind manner. Patients receiving indomethacin required significantly less opioid after operation and had significantly lower pain scores compared with the control group. Pain on movement and on coughing were reduced also. No major adverse effects were encountered.

KEY WORDS

Analgesics: indomethacin. Pain: postoperative. Surgery: thoracotomy.

Many techniques have been used for management of pain after major thoracic surgery, with varying degrees of success. The conventional use of intermittent i.m. injections of opioids is known to be less than ideal in most circumstances. I.v. infusions of opioids provide less fluctuation in the quality of analgesia, but they require the use of more sophisticated infusion devices and experienced personnel for optimal use. Cryoanalgesia is effective in decreasing opioid requirements, but is time consuming, supplies insufficient analgesia when utilized alone and may cause prolonged anaesthesia or dysaesthesia after surgery [1, 2]. Continuous paravertebral block [3, 4] and extradural analgesia using local anaesthetic or opioid may be used, but may be associated with hypotension and delayed respiratory depression [5–7]. Moreover, not all pain after thoracotomy is dermatomal in distribution and therefore may not be relieved by regional analgesia alone [8]. Interpleural local anaesthesia has been reported as being variably effective after thoracotomy [9, 10].

In recent years several studies have reported the successful use of non-steroidal anti-inflammatory agents in the treatment of postoperative pain and in the reduction in opioid requirement when used in combination with these drugs [11–13]. As such drugs might be useful in the management of pain after thoracic surgery, the use of indomethacin suppositories to augment the effects of i.v. opioid analgesia was evaluated in a prospective randomized double-blind trial.

PATIENTS AND METHODS

We studied 60 adult patients undergoing thoracotomy, after obtaining informed consent and following ethics approval by the Committee for Human Rights. Patients with a previous history of peptic ulceration were excluded from study.

Premedication comprised oral temazepam 20–30 mg 1 h before operation. Anaesthesia was induced with thiopentone and maintained with halothane or enflurane, supplemented with morphine 0.1–0.2 mg kg^{-1}. Neuromuscular block was produced with vecuronium or pancuronium, and endobronchial intubation and one-lung ventilation were undertaken when appropriate. When the patient recovered from anaesthesia, continuous i.v. infusion of papaveretum was commenced and the rate of infusion adjusted to attain adequate analgesia as determined by each individual patient. The patients were discharged from the recovery room when clinically stable and when pain was controlled satisfactorily.

The patients were allocated by random sequence to one of two study groups. One group received indomethacin suppositories after operation: two (200 mg) on termination of surgery and

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one (100 mg) twice daily for 3 days. The other group received identical placebo suppositories in a similar manner. Neither the patient nor the investigator, attending nurses and physiotherapist were aware of which drug was administered. In addition, all patients were maintained on i.v. papaveretum titrated by the attending nurse to maintain adequate postoperative pain relief as determined by the patient. The attending nurses administered bolus doses of i.v. papaveretum as required and altered the rate of infusion, increasing the rate to attain control of pain and decreasing it in the case of excessive drowsiness in the presence of adequate pain relief. The dose of bolus injections, time of administration and time and change in infusion rate were documented for all patients. All patients were nursed in the same ward by the same team of senior nurses who were experienced in administration of i.v. analgesia.

Measurements undertaken included evaluation of total requirement for papaveretum at 2, 4, 6, 12, 18, 24, 30, 36, 42 and 48 h from return to the ward and patient evaluation of pain using a 10-cm visual analogue scale [14] before and after chest physiotherapy, which was undertaken three times daily by the same physiotherapist. Chest physiotherapy involved deep breathing exercises, coughing, percussion, postural drainage and mobilization.

Statistical evaluation of papaveretum requirement was by a one-tailed t test. Comparison of pain scores was performed using the Mann–Whitney test.

RESULTS

Sixty patients were included in the study; 29 received indomethacin suppositories and 31 received placebo. Four patients receiving indomethacin suppositories were lost from study because they required transfer to the intensive care unit for surgical reasons. Two patients in the placebo groups were lost for similar reasons. Two patients were withdrawn from the study early because of suspected gastrointestinal disturbance caused by the drug. One of these patients was found to have received placebo and the other indomethacin. Patient data and the type of operation performed for the remaining patients are shown in table I.

TABLE I. *Patient data*

	Indomethacin group	Placebo group
Age (yr) (mean (SD))	60.9 (9.0)	63.7 (12.0)
Weight (kg) (mean (SD))	69.1 (12.4)	71.9 (12.8)
Sex (M/F)	19/5	15/13
Operation		
Pneumonectomy	9	13
Lobectomy	11	7
Open lung biopsy	1	6
Surgical pleurodesis		1
Excision carcinoid/ hamartoma	1	1
Excision mediastinal mass	1	
Thoracoplasty	1	

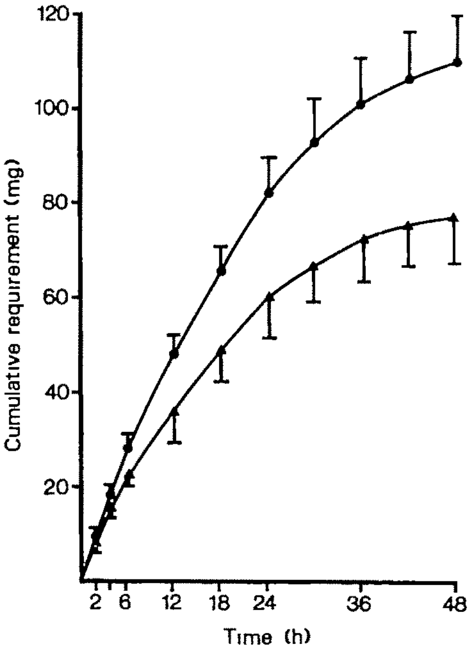

FIG. 1. Cumulative papaveretum requirement (SEM) for indomethacin (▲) and placebo (●) groups over 48 h after operation.

Patients receiving indomethacin suppositories required less papaveretum at all times compared with patients receiving placebo (figs 1, 2) ($P < 0.05$ from 12 h until completion of the study period at 48 h).

Pain scores on the first day after surgery, before and after chest physiotherapy, are shown in figure 3. Pain scores on the second day after operation followed a similar pattern.

Patients receiving indomethacin had significantly lower pain scores at all times compared with those who received placebo ($P < 0.01$). Pain scores before and after chest physiotherapy were not significantly different within each group.

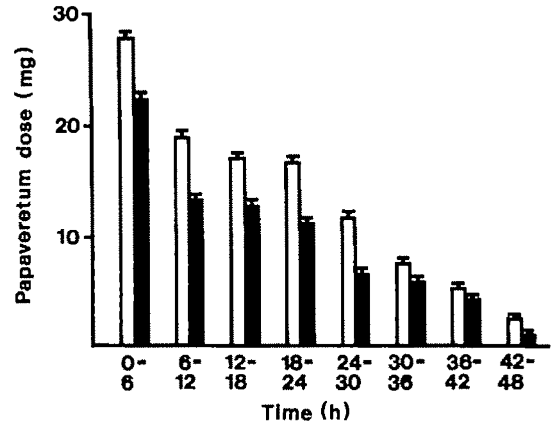

FIG. 2. Papaveretum requirements (SEM) for indomethacin (■) and placebo (□) groups in 6-h time periods for 48 h after operation.

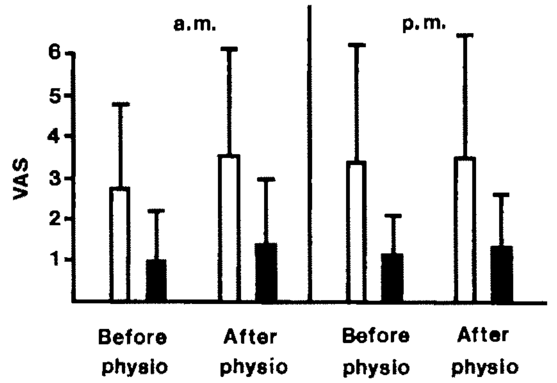

FIG. 3. Pain scores (VAS) (SD) on the first day after operation for indomethacin (■) and placebo (□) groups.

With the exception of the two patients mentioned above who were withdrawn from the study early, no other adverse effects were encountered. Indomethacin was discontinued after the third day after operation and adverse effects from its chronic use were therefore not encountered.

DISCUSSION

Non-steroidal anti-inflammatory drugs are used predominantly for mild to moderate pain. Used alone, they are usually insufficient to control pain after major surgery, but may have a significant opioid sparing effect in the immediate postoperative period. Gillies and colleagues [11] found that patients receiving ketorolac by continuous infusion required significantly less morphine than the control group after upper abdominal surgery. Similar results have been found with ibuprofen [12] and diclofenac [15].

In the present study, indomethacin significantly reduced papaveretum requirements. This may be advantageous in patients with chronic pulmonary disease at significant risk of worsening pulmonary function as a result of pulmonary resection and postoperative pulmonary atelectasis. Our results are similar to those of Reasbeck, Reasbeck and Rice [16], who studied the effect of indomethacin in patients recovering from major abdominal surgery. Keenen and colleagues [17], comparing rectal indomethacin and cryoanalgesia as adjuvants to opioid analgesia after thoracotomy, found indomethacin to be better than cryoanalgesia in reducing pain on movement. Patients receiving indomethacin alone or in combination with cryoanalgesia also required less opioid supplementation than those receiving opioid alone or opioid with cryoanalgesia.

We conclude that pain relief after thoracotomy may be improved by the administration of indomethacin, as shown by reduced pain scores and requirements for papaveretum.

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PREANAESTHETIC MEDICATION WITH CLONIDINE

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SUMMARY

The purpose of this study was to evaluate oral clonidine in a dose of 0.3 mg as a routine premedicant. Sixty-nine normotensive female patients were studied in a randomized double-blind investigation in which clonidine was compared with an inert treatment. Clonidine produced a significant reduction in anxiety ($P < 0.05$) and sedation and a reduction in the sleep dose of methohexitone ($P < 0.05$). Tachycardia in response to intubation was attenuated by clonidine ($P < 0.05$). However, the magnitude of the increase in arterial pressure after intubation was not affected. Intraoperative and postoperative hypotension were common after premedication with clonidine 0.3 mg and caution is urged in its use as a premedicant.

KEY WORDS

Anaesthetic techniques: premedication. Pharmacology: clonidine. Complications: hypotension

Premedication is used to provide sedation and anxiolysis and to enhance the quality of induction, maintenance and recovery from anaesthesia [1]. The ideal premedicant should be effective orally, analgesic and non-emetic. It should minimize side effects of the induction agent and not impair cardiovascular stability or depress respiration. In adults, anticholinergic drugs are seldom prescribed routinely but are given i.v. if specific indications exist. Alpha-2-adrenergic agonist drugs act at receptor sites in the medulla oblongata and presynaptically at peripheral nerve terminals, to cause a reduction in activity of the sympathetic nervous system, an effect which can be antagonized by α-adrenergic antagonist drugs. Recent work in animals [2] and man [3] suggests they have properties considered advantageous in premedicants. They cause sedation, analgesia, reduction in the sleep dose of induction agents and reduction in salivary secretion. Clonidine, which until now has been used mainly as an antihypertensive agent, is the only member of this drug group available for clinical use in the United Kingdom. Its use as a premedicant seemed appropriate and such a study is reported here.

PATIENTS AND METHODS

The investigation was approved by the local Medical Ethics Research Committee and each patient gave informed verbal consent.

We studied healthy women (weights 45–90 kg) in the reproductive age range undergoing pelvic laparoscopy with general anaesthesia. Those taking any other medications or with a history of drug reactions were excluded. At the preoperative visit, on the evening before surgery, heart rate and arterial pressure were recorded and the visual analogue scale (VAS) scoring system was explained. Premedication, either clonidine 0.3 mg or an inert tablet, was given orally 75–105 min before induction of anaesthesia, the treatment distribution being randomized and double-blind.

On arrival of the patient in the anaesthetic room, sedation was graded into three categories: awake and initiating conversation; awake but uncommunicative; drowsy and quiet. Anxiety was assessed by 100-mm VAS: 0 = completely calm, 100 = the worst possible anxiety.

After these assessments, a vein was cannulated and heart rate and arterial pressure were measured using the Dinamap SX 1846 and recorded at

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1-min intervals for 5 min before administration of the induction agent. Methohexitone (1 %) 1 mg kg^{-1} was given i.v. in 15 s with further increments of 0.25 mg kg^{-1} at 15-s intervals until there was loss of response to command. The total dose of the induction agent was noted. Patients were allowed to breathe spontaneously for 2 min a mixture of 70 % nitrous oxide and 2 % isoflurane in oxygen. The occurrence of involuntary muscle movement, respiratory problems (breath-holding, coughing or hiccup) was recorded and the quality of induction was graded 1, 2A, 2B or 3 according to the method of Dundee, Moore and Nicholl [4]: 1 = uncomplicated, 3 = unacceptable. Fentanyl 2 μg kg^{-1} and vecuronium 0.1 mg kg^{-1} were given i.v. and the trachea intubated 3 min later, the Bard Biomedical TOF monitor being used to ensure full muscle relaxation. Anaesthesia was maintained by IPPV with an inspired mixture of 70 % nitrous oxide and 1 % isoflurane in oxygen, ventilation being adjusted to an end-tidal partial pressure of carbon dioxide of 4.8 kPa (range 4.3–5.3 kPa) using an Engstrom Eliza Capnograph. Inspired oxygen, isoflurane concentration and arterial oxygen saturation were monitored throughout.

Following induction of anaesthesia, heart rate and arterial pressure were measured at 1-min intervals until 3 min after intubation and then at 5-min intervals until 30 min after operation. Additional measurements were made at 8 h after operation.

Postoperative pain was assessed using a 100-mm VAS 15 min after awakening or earlier if the patient requested analgesia: 0 = no pain, 100 = worst possible pain. The number of requests for analgesic treatment during a 1-h stay in the recovery ward was noted. Emetic sequelae were recorded for the first 8 h after operation.

Results are presented as mean (SD) for parametric data, and median with range for non-parametric data. Frequencies were examined with the chi-square test, non-parametric data with the Mann–Whitney *U* test and cardiovascular data were examined with analysis of variance.

RESULTS

Sixty patients were recruited initially; of these, nine were excluded because of incorrect timing of premedication, and nine other patients were recruited. The patients formed two groups of 30; one received clonidine and the other, inert medication. The two groups were broadly similar in age, weight, pre-study arterial pressure and heart rate and indication for laparoscopy (table I).

TABLE I. *Demographic characteristics, type of operation, and preoperative cardiovascular measurements (mean (SD))*

	Clonidine ($n = 30$)	Inert treatment ($n = 30$)
Age (yr)	29.4 (5.4)	31.2 (5.2)
Weight (kg)	61.3 (11)	60.6 (8.9)
Diagnostic/therapeutic	17/13	17/13
Mean arterial pressure (mm Hg)	84 (7.9)	83 (9.3)
Heart rate (beat min^{-1})	77 (4.5)	76 (7.1)

TABLE II. *Quality of induction*

Grade	Clonidine ($n = 30$)	Inert treatment ($n = 30$)
1	13	10
2A	9	8
2B	7	10
3	1	2

In the clonidine group there was significantly more sedation, five women being drowsy, nine awake and quiet and 16 talkative compared with none, three and 27, respectively, in the inert treatment series ($\chi^2 = 8.2$, df = 1, $P = 0.0042$). The median VAS score for subjective anxiety was 25 (range 0–72) and 38 (range 6–79) for clonidine and inert treatments, respectively. The lower score represents less anxiety and this difference was significant ($P < 0.05$, Mann–Whitney *U* test).

The induction dose of methohexitone required to cause loss of response to command was less in the clonidine group (1.08 (0.14) mg kg^{-1}) than in the inert treatment series (1.26 (0.25) mg kg^{-1}) ($P < 0.05$, Mann–Whitney *U* test). The induction grades are shown in table II; the quality of induction was not enhanced by clonidine premedication.

Variations in heart rate (HR) and mean arterial pressure (MAP) are shown in figure 1. After clonidine premedication, patients arrived in the anaesthetic room with a reduction in MAP of 15 mm Hg compared with control subjects. The pre-induction and intra-anaesthetic MAP were significantly less in the clonidine group compared with the inert treatment series ($P = 0.03$). Immediately before tracheal intubation, 14

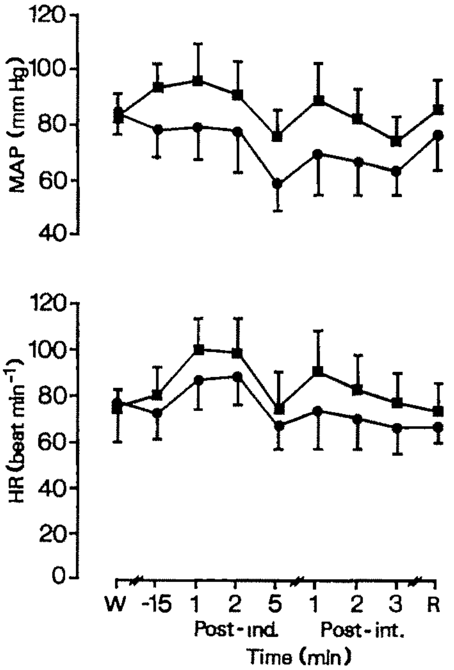

FIG. 1. Mean (SD), mean arterial pressure (MAP) and heart rate (HR) during induction of anaesthesia and surgery in the clonidine (●) and inert treatment (■) groups. ind. = Induction; int. = intubation.

of the clonidine group and none of the control group had a systolic arterial pressure of 80 mm Hg or less. Hypotension of this degree continued into the recovery period in three of the clonidine group. In both series, MAP increased with tracheal intubation, but the increases of 12 (10) mm Hg and 15 (13) mm Hg in the clonidine and control groups, respectively, were not significantly different.

In the clonidine-treated patients, pre-induction HR was reduced compared with the other group and this persisted throughout induction and maintenance of anaesthesia ($P < 0.02$). Increases in HR occurred after tracheal intubation in both groups, but were most marked in the inert treatment series (17 (15) beat min^{-1} compared with 7 (14) beat min^{-1}, respectively ($P < 0.05$)).

Postoperative VAS pain assessment, number of analgesic requests and emetic sequelae are shown in table III. None of the differences between the groups was statistically significant.

DISCUSSION

Alpha-2-adrenergic agonists have properties of potential benefit to anaesthesia [5], but their advantages and limitations require definition before they can be recommended. This investigation has attempted to evaluate clonidine as a premedicant and its effect on general anaesthesia and recovery.

No attempt was made during this study to assess the effects of clonidine on maintenance anaesthetic requirements. Arterial pressure and heart rate are affected by clonidine and these variables are therefore of less value in assessing adequacy of anaesthesia. In the absence of a specific and reliable method of measuring depth of anaesthesia, and without knowledge of the premedicant administered, we relied on a defined anaesthetic regimen to ensure adequate anaesthesia.

Clonidine in an oral dose of 0.3 mg produced both sedation and a reduction in anxiety, yet patients were responsive and free from subjective side effects. A smaller dose of the α-2-adrenergic agonist may be effective in reducing fear and nervousness without invoking the hypotension observed here.

These drugs have been found to reduce the sleep dose of thiopentone [6] and the MAC value of inhalation anaesthetics [7]. In this investigation, the sleep dose of methohexitone after clonidine premedication was reduced significantly, but the small reduction in dose of barbiturate would seem

TABLE III. *Postoperative analgesia and emetic sequelae*

	Analgesia		Emetic sequelae		
	Pain score (median (range))	No. needing morphine	None	Nausea	Vomiting
Clonidine ($n = 30$)	51 (7–100)	23	12	7	11
Inert treatment ($n = 30$)	53 (0–94)	23	8	17	5

of little clinical significance. Methohexitone was chosen as the induction agent because the incidence of involuntary muscle movement and respiratory upset is related partly to premedicant treatment [8]. After clonidine, no significant benefit was noted in the quality of the induction period.

The most important findings in this investigation related to changes in heart rate and arterial pressure. In the pre-anaesthetic period, clonidine caused a significant reduction in systolic, diastolic and mean arterial pressures, but this did not provoke any subjective symptoms in the supine patient. This confirms the findings of Wing [9], who demonstrated a 10–15 % reduction in systolic and diastolic pressure in normotensive individuals after a similar dose. Tracheal intubation initiates significant increases in arterial pressure [10] and it has been suggested that clonidine modifies this response [3, 11]. However, similar increases in arterial pressure were recorded in the clonidine and inert treatment groups, but the lower post-intubation values in the former were a reflection of the pre-existing hypotension. Clonidine 0.6 mg has been noted previously to potentiate hypotension attributable to isoflurane, although not during maintenance with 1 % isoflurane [12]. A possible explanation for this lies in the therapeutic window of clonidine, larger doses having less effect on arterial pressure [13]. The hypotensive effect of clonidine 0.3 mg continued for more than 30 min after operation in 10 % of these healthy, young patients; this precludes the use of this dose for general premedication. Clonidine reduces heart rate [14] and this was observed here. However, despite pelvic surgery, and the use of fentanyl and vecuronium (a combination which is associated frequently with bradycardia [15]), no anticholinergic treatment was required. Tachycardia may cause myocardial ischaemia in the predisposed patient [16]. In this study, the increase in heart rate in response to intubation was reduced substantially by the adrenergic agonist, which would be beneficial in patients at risk of myocardial ischaemia.

The central adrenergic system modulates pain sensation [17] and the α-2-adrenergic agonists have been shown either to provide analgesia [18] or to enhance the analgesic effectiveness of opioids. However, no reduction in severity of pain or requirement for analgesic treatment occurred during the first 1 h after operation. Pain after laparoscopy is more severe in patients who have rings, clips or diathermy applied to the fallopian tubes [19], but the distribution of these procedures was similar in the two groups. The incidence of postoperative emetic sequelae was not affected by premedication with clonidine.

Despite the pleasant anxiolytic effect of clonidine premedication, no marked advantages were demonstrated in this study. Hypotension throughout the perioperative period suggests caution in the use of clonidine 0.3 mg as a general premedicant.

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QUANTITATIVE ASSESSMENT OF EXTRADURAL BUPIVACAINE ANALGESIA

L. ARENDT-NIELSEN, B. ØBERG AND P. BJERRING

SUMMARY

Bupivacaine (0.5%) 20 ml was administered extradurally to six healthy volunteers. It was found that simultaneous application of 10 needles to the skin could evoke pain when analgesia was obtained to one needle stimulation. In addition, a laser beam was used as a quantitative technique to activate simultaneously many cutaneous nociceptors. For 7 h, thresholds (sensory and pain) and pain-evoked brain potentials (amplitude and latency) to laser stimulation were monitored and used for quantitative assessment of onset, efficacy and duration of analgesia at various dermatomes (C7, T8, T10, T12, L1, L3, S1). The onset time of analgesia was shortest and conduction delay longest at the dermatome related to the site of injection (L3). Full analgesia was obtained at L1, L3 and S1, although the peak efficacy at S1 was delayed for 120–180 min after injection. A minor effect was found at dermatome C7 approximately 60 min after injection.

KEY WORDS

Anaesthetics, local: bupivacaine. Anaesthetic techniques: extradural. Brain: evoked potentials. Nerve: laser stimulation.

The efficacy of extradural anaesthesia is dependent on such factors as age, height, anatomy and central modulating mechanisms within the central nervous system. The pinprick test is still the most commonly used technique for assessing analgesia, but its clinical relevance is debatable because it is an on–off technique, and a single needle stimulus activates only few nociceptors. This is exemplified by the clinical experience that S1 may be blocked inadequately [1] whilst analgesia is present to pinprick [2].

In this study, we have examined extradural analgesia with bupivacaine at various dermatomes by stimulation with one needle, 10 simultaneously applied needles, and laser stimulation [3, 4].

PATIENTS AND METHODS

We studied six healthy volunteers (male, mean age 26 yr, range 18–32 yr). Informed consent was obtained from all volunteers and the study was approved by the local Ethics Committee.

A Tuohy needle was inserted into the extradural space at the L2–3 interspace with the subject in a horizontal lateral position. Twenty millilitre of plain 0.5 % bupivacaine (Marcain, Astra, Sweden) was injected (0.4 ml s^{-1}) with the bevel directed cephalad, after the extradural space was identified by loss of resistance.

During the study, the volunteers were resting comfortably and wore goggles to protect against the laser light. To avoid any acoustic interference at the time of the stimulus, white noise was applied via earphones. The volunteers were asked to keep their eyes open and fix their gaze on a black spot on the ceiling.

The visible output from an argon laser (Spectra Physics, model 168, U.S.A.) was transmitted to the skin via a quartz fibre. The output power was adjusted in the range 50 mW to 3.5 W. The wavelengths were 0.488 µm (blue) and 0.515 µm (green); the distribution of the laser intensity at each wavelength was 33 % and 66 %, respectively. This distribution remained constant (±2 %) for laser intensities greater than 50–100 mW. An external laser power meter was used to measure

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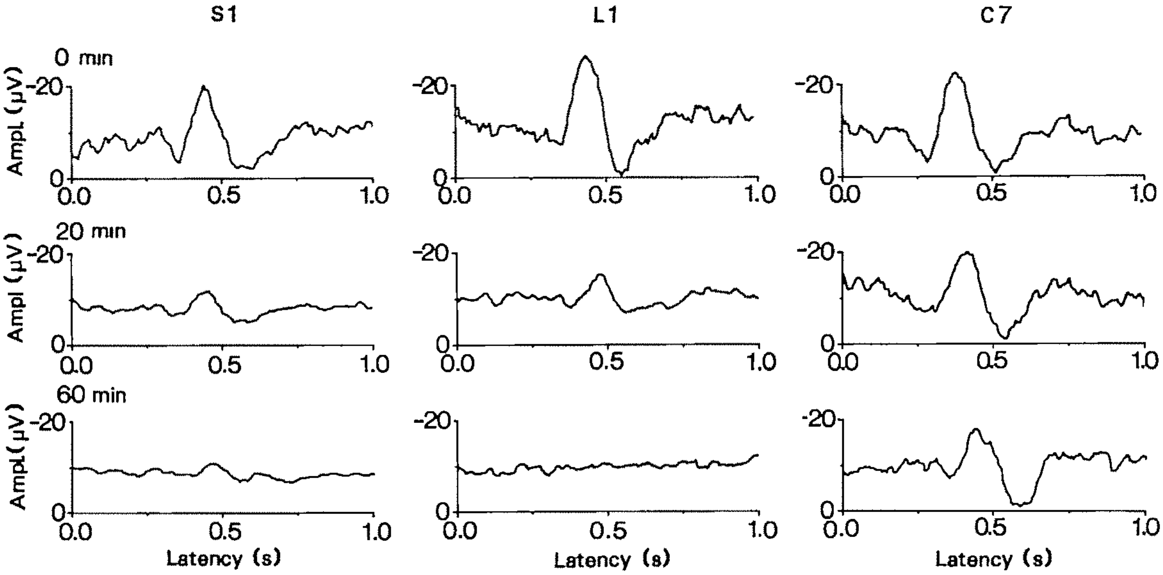

FIG. 1. Examples of the averaged laser-induced, pain-evoked potentials elicited at S1, L1 and C7 before, 20 and 60 min after analgesia. The latency and peak-to-peak amplitude (Ampl.) of the major negative complex were measured.

the dissipated output power. A continuous low energy beam (50 mW) from the argon laser visualized the stimulation site. The stimulus pulse had a duration of 200 ms and the beam diameter was 3 mm. The intervals between the stimuli were random with a mean of 10 s (range 8–12 s). The laser intensity was kept less than 3 W as greater intensities may cause minor superficial burns. Analgesia was defined as total if this level was reached.

The sensory threshold to laser stimulation was defined as a sensation of faint warmth and the pain threshold was defined as a distinct sharp pinprick. The thresholds were calculated as the mean of three ascending and three descending series of stimulation [3]. Initially, five measurements were performed to ensure the validity of the determinations.

Pain-evoked brain potentials were recorded by a platinum needle electrode (Disa 25C04), placed over the vertex with reference to linked ear lobes. The EEG was filtered by a second order filter (0.5–30 Hz), amplified 200000 times (Disa 5C01), and sampled by computer [5]. A total of 16 single potentials were averaged. Initially, two subsequent recordings were performed to ensure the validity of the recordings. The peak-to-peak amplitude and the latency of the major negative complex were used for quantification (fig. 1). If the peak-to-peak amplitude of the evoked potential was smaller than 1.2 times the maximal peak-to-peak amplitude of the averaged background EEG, 1 s before stimulation, the amplitude was assigned the value zero. Intensities from 1.5 to 2.5 W were used for stimulation. This stimulus intensity was maintained constant throughout the experiments.

One or 10 needles (18-gauge) were used for stimulation. The 10 needles were arranged symmetrically within a circle of diameter 1.5 cm. The volunteers were asked if the needle stimulation was perceived as sharp distinct pricking pain. Five subsequent stimulations were applied.

The experimental design is summarized in table I. The actual sites of stimulation within the dermatomes were selected according to the landmarks given by Griffiths and colleagues [6].

Wilcoxon's test (signed rank test) was used for analysis, and statistical significance was accepted at 5%.

RESULTS

Pain evoked by one needle stimulation was abolished at T8, T10, T12, L1 and S1 after 60 min, and the pain did not recur at T8, T10, T12 and L1 until after 240, 360, 360 and 420 min, respectively. Pain evoked by 10 needles was abolished at L1 after 60 min and at S1 after

TABLE I. *Experimental design: when and where the various sensory tests were performed after extradural injection of bupivacaine. T = Sensory and pain thresholds; EP = evoked potential; N = one and 10 needles*

	Time after extradural injection (min)										
Dermatome	0	15	20	30	45	60	120	180	240	300	360
C7	T,EP	T	EP	T	T	T,EP	T,EP	T,EP	T,EP	T,EP	T,EP
T8	T,N					T,N	T,N	T,N	T,N	T,N	T,N
T10	T,N					T,N	T,N	T,N	T,N	T,N	T,N
T12	T,N					T,N	T,N	T,N	T,N	T,N	T,N
L1	T,EP,N	T	EP	T	T	T,EP,N	T,EP,N	T,EP,N	T,EP,N	T,EP,N	T,EP,N
L3	T	T		T	T						
S1	T,EP,N	T	EP	T	T	T,EP,N	T,EP,N	T,EP,N	T,EP,N	T,EP,N	T,EP,N

120 min, and recurred at both dermatomes 300 min after extradural administration of bupivacaine.

All volunteers were analgesic to laser-induced pain at L1 and L3 30 min after injection. Only one volunteer was able to perceive the laser pulses at S1 during the entire experiment. In the other five, the laser pulses were abolished after 120–180 min (fig. 2). No subject experienced total analgesia at T8, T10 and T12 (fig. 3), and the efficacy decreased in a cephalad direction.

The rate of onset of analgesia (table II) was defined as the percentage increase in threshold 15 min after injection compared with baseline values. The onset rates at L1, L3 and S1 were faster for sensory thresholds than for corresponding pain thresholds. The fastest onset rates occurred at L3 (table II).

The pain threshold at C7 increased significantly ($P < 0.05$) 45 and 60 min after injection (fig. 2). All thresholds except that at C7 were significantly ($P < 0.05$) increased for 420 min.

Twenty minutes after extradural injection, the pain-evoked brain potentials elicited from L1 and S1 were reduced significantly ($P < 0.01$) (fig. 1, table III) by 42% and 31%, respectively. The mean amplitudes of the potentials evoked from L1 and S1 were still significantly ($P < 0.05$) reduced after 420 min (table III). The potentials evoked from C7 were significantly ($P < 0.05$) reduced 60 and 120 min after injection.

The difference in latencies measured before and 20 min after injection was larger for the potentials evoked from L1 (41%) than from S1 (37%) (table III). At S1 the maximum increment (35%) was obtained 60 min after injection.

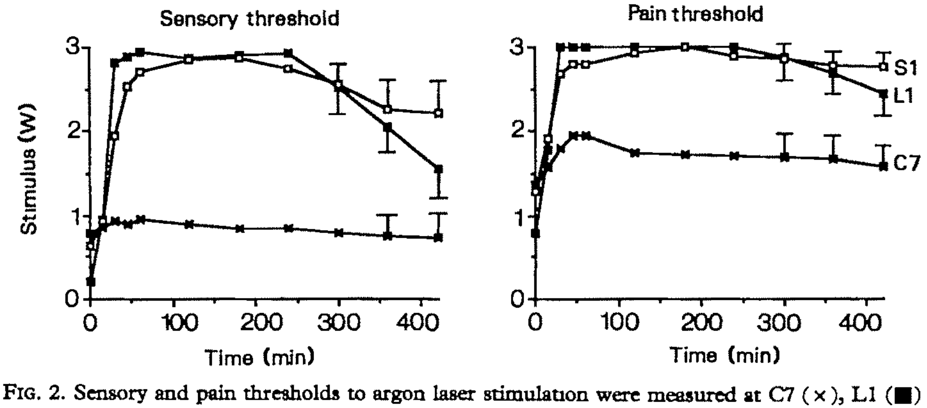

FIG. 2. Sensory and pain thresholds to argon laser stimulation were measured at C7 (×), L1 (■) and S1 (□) before and during extradural analgesia using 0.5% bupivacaine injected at the L2–3 interspace (mean values, with examples of SD). The maximal intensity used was 3 W.

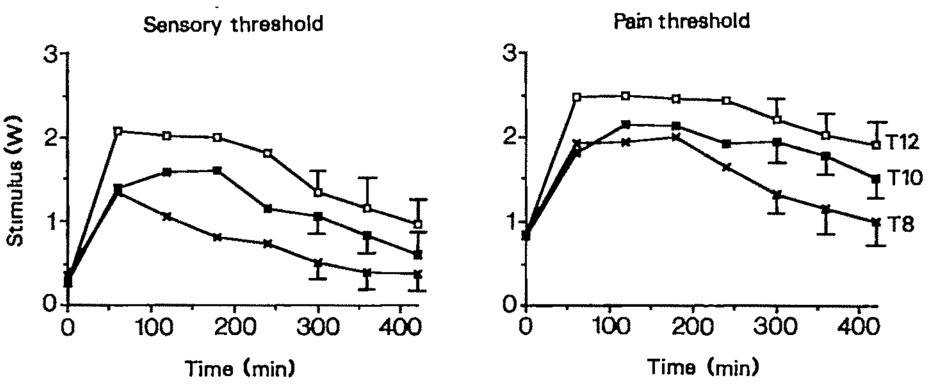

FIG. 3. Sensory and pain thresholds to argon laser stimulation were measured at T8 (×), T10 (■) and T12 (□), before and during extradural analgesia using 0.5 % bupivacaine injected at the L2–3 interspace (mean values, with examples of SD). The maximal intensity used was 3 W.

TABLE II. *Mean* (SD) (n = 6) *sensory and pain thresholds before (0) and during the first 45 min after extradural injection of bupivacaine. Thresholds were measured at C7, L1, L3 and S1. * Significant difference* (P < 0.05) *from the threshold measured before analgesia. Total analgesia is assumed at 3 W*

	Time after extradural analgesia (min)			
	0	15	30	45
Sensory threshold (W)				
C7	0.78 (0.12)	0.85 (0.15)	0.94 (0.12)	0.90 (0.12)
L1	0.25 (0.07)	0.90 (0.11)*	2.81 (0.20)*	2.89 (0.11)*
L3	0.35 (0.16)	1.80 (0.30)*	3.00 (0.0)*	3.00 (0.0)*
S1	0.64 (0.25)	0.93 (0.15)	1.94 (0.10)*	2.53 (0.12)*
Pain threshold (W)				
C7	1.37 (0.20)	1.58 (0.18)	1.79 (0.14)	1.95 (0.18)*
L1	0.78 (0.12)	1.78 (0.22)*	3.00 (0.00)*	3.00 (0.00)*
L3	0.93 (0.16)	2.31 (0.11)*	3.00 (0.00)*	3.00 (0.00)*
S1	1.35 (0.25)	1.80 (0.22)	2.68 (0.18)*	2.80 (0.09)*

DISCUSSION

Laser and needle stimulation

In addition to laser stimulation we used stimulation by means of one and 10 needles. Pain caused by one needle was blocked at a time when stimulation by 10 needles (or laser stimulation) caused pain. This suggests that stimulation by laser and by 10 needles activates central mechanisms other than those activated by one needle stimulation or that this stimulation activates non-blocked nerve fibres. These two different mechanisms correspond to spatial [7, 8] and temporal [9, 10] summation.

Sensory testing for assessment of extradural analgesia

Using the quantitative laser technique, hypoalgesia was detected at C7 approximately 60 min after injection. Occasionally, analgesia has been found to extend to the upper thoracic and even the cervical regions [11]. The weak effect at C7 could not have been detected by needle stimulation as emphasized by Kleef and Brum [12], who described the difficulties of quantifying pinprick pain when a patient experiences a needle as "sharp, but not as sharp as before". In our study, analgesia was assessed quantitatively using both thresholds and pain-evoked brain potentials. The

TABLE III. *Mean* (SD) (n = 6) *latencies and amplitudes of the major negative pain complex evoked from C7, L1 and S1 dermatomes before (0 min) and after (20–420 min) extradural analgesia. — = Could not be determined because amplitude was assigned to zero (see methods) for some of the subjects.* * *Latencies and amplitudes significantly* ($P < 0.05$) *different from the initial recordings*

	Time after extradural analgesia (min)								
	0	20	60	120	180	240	300	360	420
Latency (ms)									
C7	398	407	418	400	416	389	370	398	380
	(46)	(42)	(72)	(61)	(65)	(52)	(63)	(56)	(48)
L1	437	616*	—	—	—	—	612*	579*	545*
	(36)	(60)					(64)	(45)	(56)
S1	432	448	583*	—	—	—	550*	541*	518*
	(55)	(45)	(78)				(76)	(65)	(63)
Amplitude (μV)									
C7	38.3	34.3	30.6*	29.1*	32.0	32.9	37.8	35.4	34.8
	(6)	(8)	(8)	(7)	(7)	(8)	(6)	(5)	(8)
L1	36.5	21.1*	—	—	—	—	16.2*	17.5*	22.7*
	(12)	(9)					(10)	(12)	(9)
S1	32.2	22.2*	17.2*	—	—	—	16.2*	20.3*	23.0*
	(8)	(10)	(8)				(12)	(8)	(8)

differences between the two measurements are that thresholds provide an indication of changes in the level of excitability along the pain pathways, whereas amplitude of the pain-evoked potentials indicates how pain stimuli are perceived. The latency of the pain-evoked potential provides information on conduction velocity in the pain pathways.

Using both sensory (warmth) and pricking pain thresholds, we assumed that two nerve populations could be tested: the unmyelinated C-fibres and the thin myelinated Aδ-fibres, respectively. The most rapid onset of analgesia was found in sensory threshold, which indicated that the pattern of blocking of nerve fibres of spinal root nerves (or cord) followed the same pattern as occurs in peripheral nerves, where the thin fibres are blocked first.

Lund and colleagues [13] recorded the early somatosensory brain potentials evoked by electrical stimulation at T10, L1, S1 and to the posterior tibial nerve (PTN). Interestingly, the latency and amplitude of the S1 and PTN evoked potentials recorded 47 min after extradural injection of local anaesthetic were affected less than the responses evoked from T10 and L1. This supports the findings of Kleef and Burm [12], who demonstrated that the large afferents from S1 were conducting 40 min after administration of extradural bupivacaine. Potentials evoked by electrical stimulation therefore reflected transmission in afferent fibres, whereas the laser evoked potentials reflected small afferent fibre activity.

Experimental and clinical assessment of extradural analgesia

The onset of extradural analgesia has been investigated by Bromage [2], who obtained pinprick analgesia after 6 min at L1 and after 18 min at S1. Using laser stimulation we observed that analgesia occurred after 30 min at L1 and after 120 min at S1. The discrepancy in onset times between the two studies may be explained by central integration of the activity evoked by the laser beam. If synchronized action potentials reach the dorsal horn, even sparse activity is integrated and becomes evident to the subject. This central amplification has been utilized for diagnosis of neurological disorders [10].

For peripheral nerves, reduction in conduction velocity is related to the length of the nerve exposed to local anaesthetics [14]. If the anaesthetic in CSF affects the subarachnoid nerve roots, the latency of potentials evoked from the most caudad segments is assumed to be subject to the longest delay. As this assumption was not supported by our findings, the predominant transmission delay may occur locally around the nerve roots within the extradural space. The dorsal root ganglia are not affected by anaesthetic agents injected extradurally [15, 16]. The rapid onset at L3 may be explained by the anatomy of the spinal meninges in the region of the dural sleeves surrounding the spinal root. At this site, the dura is thin and permits rapid diffusion of local anaesthetic [17–19]. Furthermore, it has been shown that, at the site where the dorsal and ventral roots fuse, substances may diffuse readily between the subarachnoid, subdural and extradural spaces [20].

The slow onset of analgesia at S1 may be explained by two factors. First, the thickness of the S1 nerve root may be an obstacle to rapid diffusion of local anaesthetic [21]; the greater quantity of connective tissue around the S1 nerve root may also absorb a large amount of anaesthetic. Second, the injected anaesthetic spreads cephalad in the extradural space more readily than caudad because of the influence of the negative intrathoracic pressure [14].

Clinically it has been observed that inadequate analgesia may be present at L5 and S1 after extradural anaesthesia [1], although skin analgesia to pinprick is present at these dermatomes after 20 min [2]. Galindo and colleagues [21] found that 15% of their patients had inadequate block at S1 after extradural administration of 0.5% bupivacaine. This group of inadequately anaesthetized patients is currently being investigated at our laboratory using the techniques described in this study.

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ONSET PHASE OF SPINAL BUPIVACAINE ANALGESIA ASSESSED QUANTITATIVELY BY LASER STIMULATION

L. ARENDT-NIELSEN, E. ANKER-MØLLER, P. BJERRING AND N. SPANGSBERG

SUMMARY

Analgesia was assessed quantitatively at various dermatomes (C7, T8, T10, T12, L1, L3, S1) for the first 30 min after subarachnoid administration of 0.5% bupivacaine 3.5 ml. Stimulation with 10 needles and laser stimulation could evoke pain in dermatomes with adequate analgesia to single needle stimulation. Analgesia was assessed by thresholds (sensory and pain) and by pain-related brain potentials (amplitude and latency) to laser stimulation. Little analgesia was found at T10, but it increased gradually towards caudal segments. The dermatome related to the site of the injection (L3) was not blocked to a greater extent than the surrounding dermatomes. Conduction time (the latency of the evoked brain potential) was increased relatively more from the S1 dermatome compared with L1.

KEY WORDS

Anaesthetics, local: bupivacaine. Anaesthetic techniques: spinal. Brain: evoked potentials.

It is known that tourniquet pain may develop during spinal analgesia in patients with adequate analgesia to pinprick [1, 2], and that brain potentials can be elicited by stimulation of dermatomes with full pinprick analgesia [3]. Examination of this difference between clinical observations and the sensory tests used for assessment of spinal analgesia has been hampered by lack of quantitative techniques to evaluate the state of the nociceptive system. In an accompanying study [4] we used several quantitative sensory tests to investigate the importance of pain stimulus and regional variations during extradural analgesia with bupivacaine. In this study we have investigated the importance of these factors during the onset phase of spinal analgesia with bupivacaine.

PATIENTS AND METHODS

We studied eight patients (six male, mean age 61 yr; two female, mean age 63 yr). The patients had no signs of neurological disorders and were undergoing transurethral resection. None of the patients received premedication, and none had been exposed to laser stimulation previously. Informed consent was obtained from all patients and the study was approved by the local Ethics Committee.

The patients were placed in a lateral horizontal position. Dural puncture was performed with a 25-gauge spinal needle at the L3–4 interspace via a standard midline approach. When free flow of cerebrospinal fluid was obtained, the bevel was directed cephalad, and 0.5% plain bupivacaine 3.5 ml was injected without barbotage. Immediately after the needle was withdrawn, the patient was turned to a supine horizontal position.

The methods of evaluating analgesia are described in the accompanying paper [4] and the experimental design is summarized in table I. The design was determined by the time required for the individual sensory tests.

Wilcoxon's test (signed ranks test) was used for statistical analysis, and statistical significance was accepted at 5%.

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TABLE I. *Experimental design: when and where the various sensory tests were performed after the spinal injection of bupivacaine. T = Sensory and pain thresholds; EP = evoked potential; N = one and 10 needles*

	Time after spinal injection (min)					
Dermatome	0	5	7	10	15	30
C7	T, EP	T	EP	T	T, EP	T, EP
T8	T, N					T, N
T10	T, N					T, N
T12	T, N					T, N
L1	T, EP, N	T	EP	T	T, EP	T, EP, N
L3	T	T		T	T	T
S1	T, EP, N	T	EP	T	T, EP	T, EP, N

TABLE II. *Mean (n = 8) laser intensities for the sensory and pain thresholds determined at C7, L1, L3 and S1 before and after (5, 10, 15, 30 min) spinal administration of 0.5% bupivacaine 3.5 ml. * Significant (P < 0.05) changes compared with the values before analgesia. Total analgesia is assumed at 3 W*

Time (min)	Sensory threshold (W)				Pain threshold (W)			
	C7	L1	L3	S1	C7	L1	L3	S1
0	0.69	0.94	0.81	0.82	1.21	1.56	1.41	1.40
5	0.67	1.69*	2.20*	2.80*	1.20	2.21	2.59*	2.95*
10	0.72	2.20*	3.00*	2.93*	1.17	2.54*	3.00*	3.00*
15	0.72	2.40*	3.00*	3.00*	1.22	2.56*	3.00*	3.00*
30	0.74	2.40*	3.00*	3.00*	1.22	2.51*	3.00*	3.00*

TABLE III. *Mean (n = 8) (SD) peak-to-peak amplitudes and the latencies of the pain-related brain potentials evoked from C7, L1 and S1 dermatomes before, 7, 15 and 30 min after spinal injection of bupivacaine. — = Potentials could not be recorded from all eight patients. * Significant (P < 0.05) changes compared with the value before analgesia*

	Amplitude (µV)				Latency (ms)			
	Time after injection (min)				Time after injection (min)			
Dermatome	0	7	15	30	0	7	15	30
C7	21.0 (3.2)	19.2 (4.1)	18.5 (3.2)	18.0 (4.5)	405 (50)	402 (56)	396 (70)	380 (63)
L1	22.3 (5.1)	15.7* (5.2)	—	—	446 (45)	481* (56)	—	—
S1	17.5 (4.5)	10.1* (4.0)	—	—	451 (74)	537* (68)	—	—

RESULTS

Thirty minutes after injection, the pinprick pain evoked by one needle was abolished at T10, T12, L1 and S1, whereas analgesia to insertion of 10 needles was obtained at L1 and S1. In two patients, pain could be elicited at L1 by 10 needles. The laser pulses were abolished at L1 30 min after injection in all patients except one.

The rate of onset of analgesia was defined as the percentage increase in laser thresholds 5 min after injection. The onset rates of analgesia for sensory thresholds at L1, L3 and S1 were 79%, 171% and 250%, respectively. For pain threshold, the corresponding values were 41%, 83% and 110%. The sensory and pain thresholds determined at C7 varied 3.0% and 1.7% (coefficient of variance), respectively, and no significant changes were found. The thresholds are summarized in table II.

The significant ($P < 0.05$) reductions in amplitude (table III) at L1 and S1, obtained 7 min after injection, were 29 % and 43 %, respectively. The variation in the amplitude between the two subsequent initial recordings varied from 8 to 18 %. After 15 min it was impossible to evoke any detectable responses at L1 and S1. The latencies 7 min after spinal injection were prolonged significantly by 8 % at L1, and by 19 % at S1 (table III). The potentials evoked from C7 remained constant.

DISCUSSION

In the present study we investigated a small number of dermatomes at various times, and so we were not able to provide a detailed description of spread and onset of analgesia. Determination of pain thresholds to laser stimulation is easy and fast to perform and provides information on the efficacy of anaesthetic block. Recordings of evoked brain potentials are more time-consuming, but provide information on efficacy of block and changes in conduction velocity along the pain pathways. When combined, the techniques provide a quantitative description of onset, efficacy and spread of extradural and spinal analgesia.

One needle, 10 needles and laser stimulation

The patients perceived the argon laser pulses as distinct, unexpected and more painful compared with 1- and 10-needle stimulation. One explanation for this may be that the afferent volley evoked by a laser pulse is not contaminated with impulses evoked by touching the skin. The skin area activated by a laser beam is much larger than the area activated by an 18-gauge needle.

Within the same dermatome, the size of the area exposed to pain, and hence the number of receptors activated, was found to be as important during the onset phase of spinal analgesia as for extradural analgesia with bupivacaine [4]. Spatial [5, 6] and temporal [7, 8] summation of the activity from partly anaesthetized or surviving nociceptive nerve fibres may explain why skin incisions can be felt, at a time when there is analgesia to one-needle stimulation. This might explain also why pain may occur in the presence of a tourniquet in patients with adequate analgesia to one-needle stimulation [2]. Inability to predict adequate spinal analgesia using conventional pinprick tests has been emphasized previously [2].

Inhibition of laser-induced pain

Many investigators have determined the time to onset of pinprick analgesia following spinal administration of bupivacaine. It is generally accepted that L1 and L3 are blocked after 4–6 min [9] under conditions similar to those in the present study. A period of 10–15 min should elapse before sufficient analgesia to laser stimulation was obtained at L1, L3 and S1. The rate of onset of analgesia (increase in thresholds) was greatest at S1, followed by L3 and finally L1, indicating that the dermatome corresponding to the site of injection (L3–L4) is not blocked more efficiently than the surrounding dermatomes. The injected anaesthetic agent affects the neural components within the spinal cord and the subarachnoid nerve roots, but the importance of these two sites of action is unknown.

It would be expected that the degree of analgesia would be proportional to the length of the nerve roots exposed to anaesthetic agent. Studies on peripheral nerves have confirmed this relationship [10]. Our findings support this observation, as the efficacy and onset rate of analgesia (measured by thresholds, amplitude and latency) within the first 10 min were greater at S1 than L1.

The CSF concentration of anaesthetic after subarachnoid administration decreases gradually in a cephalad direction [11]. This would also contribute to a greater effect on the ascending S1 roots compared with L1 roots.

Sensory tests for assessment of spinal analgesia

Attempts have been made to study the effect of spinal analgesia on various neural structures by testing the sequence of block of different sensory nerve populations. After spinal injection of bupivacaine, thermal (C-fibres) discrimination is blocked very rapidly [9], followed by block of pinprick pain (Aδ-fibres) and finally perception of touch (Aβ-fibres) [2]. This indicates that block of somatic nerve fibres within the subarachnoid space or the ascending tracts follows the same pattern as that in peripheral nerves exposed to local anaesthetic [10]. In this study we found that the threshold for warmth (C-fibres) increased twice as fast shortly after spinal injection as the threshold for pricking pain (Aδ-fibres), which is in agreement with the pattern described previously.

Lund and colleagues [3] found that the early somatosensory brain potentials evoked by electrical dermatomal stimulation could be evoked from the pinprick-anaesthetized dermatomes L1 and S1 15 min after spinal injection of bupivacaine. This emphasizes that the largest nerve fibres, which are elicited by electrical pulses, still conduct action potentials, while laser-induced pain is blocked. It is not known if the central integration of activity from large surviving mechanosensitive nerve fibres causes unpleasant sensation. However, it has been suggested that the unpleasant and very painful cold pressor test, in which the hand is immersed into ice water, is also associated with activity in the mechanosensitive afferents [12]. Using amplitudes and latencies of both electrically evoked and laser evoked brain potentials, it should be possible to differentiate between large and small fibre block.

ACKNOWLEDGEMENTS

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EFFECTS OF 2% LIGNOCAINE ON SOMATOSENSORY EVOKED POTENTIALS RECORDED IN THE EXTRADURAL SPACE

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SUMMARY

We have studied the effects of extradural administration of 2% lignocaine at the L3–4 interspace on somatosensory evoked potentials recorded in the cervical extradural space before corrective surgery for idiopathic adolescent scoliosis. Eight patients in whom the equivalent volume of 0.9% sodium chloride solution was administered into the lumbar extradural space acted as a control group. Lignocaine 2% resulted in a decrease in overall amplitude, but its main effect was a significant decrease in the amplitude of the second and third peaks, suggesting an action on the dorsal columns of the spinal cord. A significant increase in latency was found in both the lignocaine and sodium chloride groups. We conclude that the use of extradural 2% lignocaine in patients undergoing scoliosis surgery may interfere with the intraoperative monitoring of somatosensory evoked potentials.

KEY WORDS

Anaesthetics, local lignocaine. Anaesthetic techniques· extradural Monitoring: somatosensory evoked potentials

Monitoring of the somatosensory evoked potentials (SEP) to posterior tibial nerve stimulation is the method of choice for assessing the integrity of the spinal cord during scoliosis surgery [1]. Despite the reliability of this method over several years [2, 3], there are instances of neurological damage occurring without any change in the SEP [4]. Thus a condition of anaesthesia for scoliosis surgery is that the patient is awake and co-operative soon after completion of the surgery so that any neurological deficit may be detected and appropriate action taken. Additional requirements include the provision of controlled hypotension and alleviation of severe postoperative pain.

The use of extradural analgesia would meet these anaesthetic considerations for scoliosis surgery if local analgesics did not interfere with the intraoperative monitoring of the SEP. Therefore, in the present study we have examined the effects of 2% lignocaine 10 ml on the SEP to posterior tibial nerve stimulation recorded in the extradural space. We chose this large dose of lignocaine, 200 mg, to determine the maximal effect on the SEP.

PATIENTS AND METHODS

We studied 24 patients (21 female, three male) admitted to the Royal National Orthopaedic Hospital for corrective surgery for idiopathic adolescent scoliosis. All patients had a scoliosis which was concave to the left with a Cobb angle between 30° and 70° as assessed by plain erect x-rays. The study was approved by the Hospital Ethics Committee and written, informed consent was obtained from the patients, or the parents, as appropriate. Patients were allocated randomly to one of three groups. A control group received a general anaesthetic without extradural analgesia. A second group received the same general anaesthetic together with 2% lignocaine extradurally and a third group received the same

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general anaesthetic and extradural 0.9% sodium chloride solution.

All patients were premedicated with papaveretum 0.3 mg kg^{-1} and hyoscine 0.006 mg kg^{-1} i.m. 90 min before induction of anaesthesia. Anaesthesia was induced with propofol 2.5 mg kg^{-1} and tracheal intubation facilitated with pancuronium 0.08 mg kg^{-1}. The lungs were ventilated with 70% nitrous oxide in oxygen and a radial artery cannulated for the measurement of arterial pressure. The patients were placed in a prone position on a Montreal mattress and the extradural space located at the C7–T1 interspace using a 15-gauge modified Tuohy needle and the hanging drop technique. A 3-French gauge bipolar recording electrode was passed through the needle cephalad and connected to the preamplifier of a Medelec MS 91 electromyograph recorder.

The right and left posterior tibial nerves were stimulated alternately via skin surface electrodes using square-wave impulses of 0.2 ms duration at an intensity of 150 μV. The stimulation frequency was 20 s^{-1} and a minimum of 750 responses were averaged with a resolution of 0.033 ms. After the measurement of the baseline SEP those patients in the extradural groups received either 2% lignocaine 10 ml at the L3–4 interspace (extradural lignocaine group) or 0.9% sodium chloride 10 ml at the L3–4 interspace (extradural saline group) using a single-shot technique. A three-stage infusion of propofol was started in all patients: 21 mg kg^{-1} h^{-1} for 5 min, 12 mg kg^{-1} h^{-1} for 10 min and 6 mg kg^{-1} h^{-1} thereafter. This infusion regimen has been shown to result in blood concentrations of propofol of approximately 4 μg ml^{-1} at 30–50 min after the start of the infusion [5].

SEP measurements from the cervical extradural space to alternate posterior tibial nerve stimulation were made 30, 40 and 50 min after the extradural injection (extradural lignocaine and saline groups) or start of infusion of propofol (propofol control group). At each time point three SEP, each of 750 responses, were made from each leg and mean arterial pressure was measured. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 3.5–4.0% and the rectal temperature remained greater than 35 °C. In the extradural lignocaine group, Hartmann's solution was infused i.v. to maintain a mean arterial pressure greater than 70 mm Hg. At the end of the investigation the patient was taken into theatre and surgery commenced. The extradural electrode was then used to monitor the SEP during the corrective surgery.

The evoked potentials were analysed for first peak latency, overall amplitude and amplitude of the first, second and third peaks. The neurophysiological data are presented as medians and ranges; because of the skewed distribution of the data, statistical evaluation was undertaken using the Wilcoxon signed rank test and the Mann–Whitney *U* test.

RESULTS

Mean (SD) age and body weight were similar in the three groups: extradural lignocaine 18.5 (4.4) yr and 52.7 (4.0) kg; extradural saline 16.7 (3.2) yr and 51.3 (10.5) kg and propofol control 18.4 (4.2) yr and 54.8 (7.9) kg.

There was no significant difference between the extradural saline and propofol control groups for any of the neurophysiological variables. For the sake of clarity, therefore, data are presented only for the extradural lignocaine and saline groups.

Typical SEP after the extradural administration of 2% lignocaine 10 ml are shown in figure 1. The important changes were a decrease in overall amplitude and second and third peak amplitudes. These were present after 30 min and sustained at

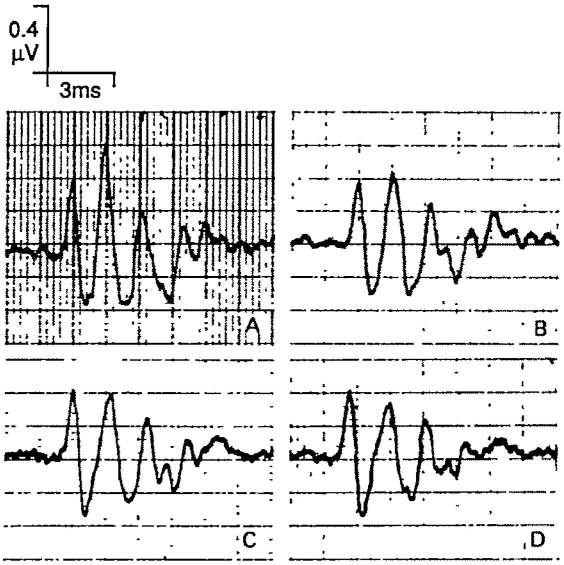

FIG. 1. Effects of 2% lignocaine 10 ml on the somatosensory evoked potential to posterior tibial nerve stimulation recorded in the cervical extradural space. A: Baseline; B: 30 min after lignocaine; C: 40 min after lignocaine; D: 50 min after lignocaine.

TABLE I. *Median (range) overall amplitude of SEP (μV) in patients receiving either extradural 2% lignocaine or extradural saline. Significant difference between groups*: *P < 0.05

Time (min)	Left leg		Right leg		
	Lignocaine (n = 8)	Saline (n = 8)	Lignocaine (n = 8)		Saline (n = 8)
0	0.86	0.97	1.01		1.57
	(0.63–2.37)	(0.65–3.05)	(0.67–1.17)		(0.36–2.00)
30	0.76	1.13	0.72	*	1.54
	(0.57–2.23)	(0.79–2.88)	(0.38–0.91)		(0.36–2.32)
40	0.66	1.17	0.74		1.53
	(0.55–2.13)	(0.81–2.87)	(0.24–0.94)		(0.34–2.33)
50	0.67	1.12	0.69	*	1.53
	(0.52–2.03)	(0.80–2.68)	(0.24–0.91)		(0.35–2.55)

TABLE II. *Median (range) second peak amplitude (μV) in patients receiving either extradural 2% lignocaine or extradural saline. Significant difference between groups*: *P < 0.05

Time (min)	Left leg			Right leg		
	Lignocaine (n = 8)		Saline (n = 8)	Lignocaine (n = 8)		Saline (n = 8)
0	0.55		0.78	0.84		0.79
	(0.40–2.22)		(0.61–2.82)	(0.40–0.85)		(0.19–1.43)
30	0.41		0.81	0.48	*	1.00
	(0.09–1.48)		(0.68–2.47)	(0.10–0.96)		(0.17–1.30)
40	0.41	*	0.75	0.51	*	1.15
	(0.09–0.83)		(0.63–2.43)	(0.12–0.86)		(0.19–1.19)
50	0.30	*	0.75	0.51	*	1.10
	(0.13–0.93)		(0.68–2.37)	(0.12–0.91)		(0.16–1.20)

TABLE III. *Median (range) third peak amplitude (μV) in patients receiving either extradural 2% lignocaine or extradural saline. Significant difference between groups*: *P < 0.05; **P < 0.01

Time (min)	Left leg			Right leg		
	Lignocaine (n = 8)		Saline (n = 8)	Lignocaine (n = 8)		Saline (n = 8)
0	0.63		0.66	0.62		0.93
	(0.22–0.98)		(0.34–1.31)	(0.29–0.83)		(0.24–1.67)
30	0.40	**	0.71	0.41		0.89
	(0.25–0.53)		(0.40–1.43)	(0.21–0.61)		(0.25–1.67)
40	0.36	**	0.67	0.39	*	0.89
	(0.21–0.52)		(0.43–1.45)	(0.23–0.70)		(0.25–1.34)
50	0.38	**	0.67	0.36		0.79
	(0.23–0.48)		(0.41–1.47)	(0.11–0.65)		(0.23–1.37)

40 and 50 min. There was little change in first peak amplitude.

Overall amplitude

Overall amplitude decreased after administration of lignocaine (table I), but this change was significant only for the right leg at 30, 40 and 50 min ($P < 0.05$). Extradural saline had no effect on overall amplitude; a significant difference between the extradural groups was found for the right leg only at 30 and 50 min ($P < 0.05$).

Individual peak amplitudes

There was no significant effect of lignocaine on the amplitude of the first peak and no significant differences between the groups (results not shown). Extradural lignocaine resulted in a significant decrease in second peak amplitude in both

TABLE IV. *Median (range) latency (ms) in patients receiving either extradural 2% lignocaine or extradural saline. No significant difference between the groups during the study*

Time (min)	Left leg		Right leg	
	Lignocaine ($n = 8$)	Saline ($n = 8$)	Lignocaine ($n = 8$)	Saline ($n = 8$)
0	14.5 (12.9–15.5)	15.0 (14.0–16.0)	14.5 (13.6–15.2)	15.2 (14.2–16.6)
30	15.2 (13.8–16.4)	15.7 (14.3–16.4)	15.4 (14.2–16.0)	15.6 (14.4–16.8)
40	15.5 (14.4–16.9)	15.7 (14.3–16.4)	15.8 (14.6–16.3)	15.7 (14.5–16.8)
50	15.6 (14.4–17.0)	15.8 (14.4–16.4)	16.1 (14.8–16.7)	15.8 (14.5–16.8)

legs (left leg, $P < 0.05$ at 30 min and $P < 0.01$ at 40 and 50 min; right leg, $P < 0.05$ at 30 and 40 min) (table II). There was a significant difference between the extradural lignocaine and saline groups for the left leg at 40 and 50 min ($P < 0.05$) and for the right leg at 30, 40 and 50 min ($P < 0.05$). A similar pattern of change was seen for the third peak amplitude (table III). Lignocaine produced a significant decrease in amplitude for the left leg at 30 and 50 min ($P < 0.05$) and 40 min ($P < 0.01$), but only at 50 min ($P < 0.05$) for the right leg. Again this resulted in a significant difference between the groups at 30, 40 and 50 min for the left leg ($P < 0.01$) and for the right leg only at 40 min ($P < 0.05$).

Latency increased significantly ($P < 0.05$) throughout the study in all groups at 30, 40 and 50 min and there was no significant difference between the groups at any time (table IV). Mean arterial pressure decreased similarly in the three groups. During the period of measurement of the SEP mean arterial pressure was between 76 and 79 mm Hg in the extradural lignocaine group and between 80 and 83 mm Hg in the extradural saline group. There was no significant difference between the groups.

DISCUSSION

The major finding of the study was that administration of 2% lignocaine 10 ml into the lumbar extradural space resulted in a decrease in the SEP recorded in the cervical extradural space. The L3–4 site was chosen so that the maximal effect of lignocaine on the stimulation of the posterior tibial nerve could be studied. Although overall amplitude decreased, the most important feature was a decline in amplitude of the second and third peaks. The first peak of the SEP represents conduction in the anterolateral tracts at 65–80 m s^{-1}, while the later two peaks represent slower transmission in the dorsal column [2]. Our results suggest that extradural lignocaine depressed conduction in the dorsal column selectively. This is surprising, as dorsal column transmission is largely asynaptic, whereas the first peak, which was unaffected, involves some synaptic transmission. It is possible that the apparent selectivity of lignocaine for the dorsal column reflected a direct effect of the drug on superficial sites in the spinal cord. It is noteworthy that 2% lignocaine did not abolish the SEP in any patient, indicating that afferent sensory transmission was preserved even when sufficient lignocaine was given to achieve good clinical analgesia.

The only comparable clinical work is that of Saugbjerg and colleagues [6], who investigated the effects of 0.5% bupivacaine 10 ml injected into the lumbar extradural space on the SEP, recorded using scalp electrodes, to posterior tibial nerve stimulation. Their results suggested that bupivacaine suppressed the early components of the SEP and increased the latency of the first peak.

As the first peak of the SEP recorded cranially is considered to represent dorsal column activity [7], our data on amplitude are compatible with the findings of Saugbjerg and colleagues [6]. However, they studied only six patients and did not include a control group. The lack of a control group is of particular importance, as these authors noted an increase in first peak latency after bupivacaine. In the present study, we observed a similar increase in latency in all three groups, which was related possibly to the slow cooling of the spinal cord [8]. Thus changes in latency of the SEP cannot be ascribed to the actions of a local analgesic in the absence of a suitable control group.

We observed a greater effect of lignocaine on the second and third peak amplitudes after left leg rather than right leg stimulation (tables II and III). This laterality of effect was noted in a previous study examining the action of halothane on the SEP [9] and has been described by others also [10]. It is likely that this finding reflects the surgical model studied, idiopathic adolescent scoliosis, in which the spinal curve is almost invariably concave to the left. The possible occurrence of this laterality in scoliosis patients is missed if only one leg is stimulated or both legs stimulated concurrently [11].

The most likely explanation for the effects of lignocaine in modulating the SEP is that the local analgesic inhibits afferent transmission in the nerve roots. It is possible that lignocaine also alters the evoked potential by decreasing spinal cord blood flow. Experimental studies in dogs have yielded equivocal data, with either no effect or an increase in cord blood flow after subarachnoid lignocaine [12, 13], and a decrease in blood flow after extradural lignocaine [14]. In the study of extradural lignocaine Mitchell and colleagues [14] found that a loss of the SEP occurred concurrently with a decrease in cord blood flow in the lumbar region. However, their data also show that there was no difference in cord blood flow between dogs given either extradural lignocaine or saline. We consider it unlikely, therefore, that our results may be attributed to a direct effect of lignocaine on spinal cord blood flow.

For extradural lignocaine to be used in patients undergoing scoliosis surgery, this technique must not interfere with the intraoperative monitoring of the SEP. A loss of more than 50% of overall amplitude, or the complete loss of one peak, is used commonly to indicate neurological damage [1]. The peaks were always present after lignocaine, although significantly decreased, but three of the eight patients showed a decrease in overall amplitude greater than 50% at some point during the study. It is probable that this represents the maximal effect of extradural lignocaine 200 mg on the SEP to posterior tibial nerve stimulation, and that lignocaine may have less effect at smaller concentrations and other sites such as the mid-thoracic region.

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COMPARISON OF FOUR LOCAL EXTRADURAL ANAESTHETIC SOLUTIONS FOR ELECTIVE CAESAREAN SECTION†

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SUMMARY

We have examined a combination of two local anaesthetics to see if the resultant solution is superior to the agents individually. This study shows that a mixture of bupivacaine and lignocaine provided an excellent alternative to bupivacaine alone, and was superior to 2% lignocaine with adrenaline for elective Caesarean section. By reducing the dose of bupivacaine used, the combination may reduce the risk of cardiotoxicity.

KEY WORDS

Anaesthesia: obstetric. Anaesthetics, local: bupivacaine, lignocaine. Anaesthetic techniques extradural

Extradural anaesthesia is a popular technique for Caesarean section and is preferred to general anaesthesia by many patients. Its use has been advocated as the technique of choice in the latest report on maternal deaths as it avoids the risks of general anaesthesia [1].

Paramount amongst the requirements of extradural anaesthesia are maternal and fetal safety, followed closely by reliability of the block. The ideal agent would produce a block of rapid onset, good quality and adequate duration, with a minimum of toxic effects to mother or baby.

Plain 0.5% bupivacaine solution has been the standard agent for Caesarean section in the U.K. for many years, but the addition of 1:200000 adrenaline has been shown to improve the efficacy of the block [2] and to prolong its duration of action [3]. Reynolds, Hargrove and Wyman showed that the addition of adrenaline reduced the maternal plasma concentration of bupivacaine during labour [4], although this was not the finding of Wilson and colleagues at Caesarean section [3]. Lignocaine 2% has been used widely in the U.S.A. Early reports that it caused neonatal depression [5] have not been substantiated, and Abboud and her co-workers have shown 2% lignocaine was a safe and effective alternative to 0.5% bupivacaine, especially when adrenaline 1:200000 was added [6]. The same workers found that the onset of action of plain lignocaine was delayed by addition of adrenaline, but that the quality of the block was improved.

Mixtures of local anaesthetic agents have been used for several years in non-obstetric practice, to utilize the beneficial properties of both agents. In addition, reducing the dose of bupivacaine may reduce the risk of its cardiotoxicity [7].

We have compared a 50:50 mixture of 2% lignocaine and 0.5% bupivacaine with adrenaline ("the mixture") with the three other solutions in common use in the U.K., to determine if the onset time or quality of block produced by the mixture showed any clinical advantages.

PATIENTS AND METHODS

We studied 80 healthy women presenting for elective Caesarean section under extradural anaesthesia after Ethics Committee approval and informed patient consent had been obtained. Mothers with pre-eclampsia or pre-term deliv-

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eries were excluded. Subjects were allocated randomly to receive one of the four solutions under study: 0.5% bupivacaine plain (B), 0.5% bupivacaine with 1:200000 adrenaline (B+A), 2% lignocaine with 1:200000 adrenaline (L+A), or a 50:50 mixture of 0.5% bupivacaine and 2% lignocaine with 1:200000 adrenaline (mixture). Adrenaline was added freshly to the plain preservative-free solutions, where appropriate, as 0.1 ml of 1:1000 adrenaline to each 20 ml, in order to keep the pH of each solution similar. The mixture was made up by adding 10 ml of plain 0.5% bupivacaine to 10 ml of plain 2% lignocaine, and adding adrenaline as described. All solutions were used at room temperature, and there was no attempt to adjust the pH. A maximum of 40 ml of test solution was available to each patient.

The study was performed in a double-blind manner, and each solution was prepared freshly by a second anaesthetist who was not involved directly in the anaesthetic or testing of the patient.

Following routine prophylaxis with ranitidine and oral antacid, cannulation of a vein and non-invasive cardiovascular monitoring, the patient was placed in the left lateral position. The extradural space was located by a 16-gauge Tuohy needle at the L2–3 or L3–4 interspace with the loss of resistance to saline technique, and 3 cm of catheter was left in the space.

After an i.v. preload of Hartmann's solution 1 litre, 3 ml of the test extradural solution was injected through the catheter with the patient in the left lateral position. After 5 min, with no sign of catheter misplacement, a further 17 ml of test solution was injected over 2 min. Five minutes after the end of this main injection, the patient was turned to the right lateral position. Arterial pressure and heart rate were recorded every 5 min, as was the progress of the block. Sympathetic block was assessed by the presence of warm and vasodilated feet, sensory block by the loss of cold sensation with ethyl chloride spray, and motor block by loss of leg muscle power on a four-point Bromage scale. If, 20 min after the end of the main injection, the thoracic or sacral sensory level was considered inadequate, further increments of the same solution were given and the patient's position changed, as deemed appropriate.

In all patients ephedrine 60 mg was added to the second 1 litre of Hartmann's solution. Hypotension was minimized by infusing this solution to ensure that the systolic arterial pressure was maintained greater than 100 mm Hg or more than 80% of the pre-extradural value.

Surgery was permitted only when the anaesthetist considered that the block was adequate in density and spread. An upper sensory level of T4 and a lower level of S5 were considered appropriate. The onset time was defined as the time from giving the test dose to the patient being ready for surgery, as assessed by the anaesthetist. Any pain or discomfort during the procedure was treated by inhalation of Entonox (a 50:50 mixture of oxygen and nitrous oxide), supplementary extradural solution, or i.v. or extradural opioids after delivery of the baby.

Maternal blood samples were taken also at specific times, for measurement of plasma concentrations of local anaesthetic, as was cord blood at delivery.

The progress of motor and sensory blocks was checked at 1-h intervals in the postoperative period, and the mothers were given extradural diamorphine analgesia (0.06 mg kg^{-1}, to a maximum of 5 mg) when the upper sensory level had regressed by three segments. One hour after the end of surgery, both anaesthetist and patient were asked to answer preset questions to evaluate the extradural.

Statistical analysis

To compare the four anaesthetic groups, analysis of variance techniques were used. For continuous variables the parametric form was used, but for discrete variables the non-parametric Kruskal–Wallis analysis of variance was used. A chi-square test was also used where appropriate. $P < 0.05$ was regarded as statistically significant.

RESULTS

The groups were comparable for patient age (mean 33.0 (SD 5.1) yr) and weight (77.0 (SD 12.1) kg), and duration of surgery (mean 47.1 (SD 10.5) min).

There was no significant difference in the volumes of extradural solution used in each group (B: 24.2 (SD 4.3) ml; B+A: 22.3 (SD 3.7) ml; L+A: 26.4 (SD 7.2) ml and mixture: 23.5 (SD 5.4) ml). The overall mean volume used was 24.0 (SD 5.5) ml. Fewer patients given bupivacaine with adrenaline or the mixture required supplementary top-ups than in the other groups, although the difference was not significant (fig. 1). There was no symptomatic evidence of systemic toxicity in any patient.

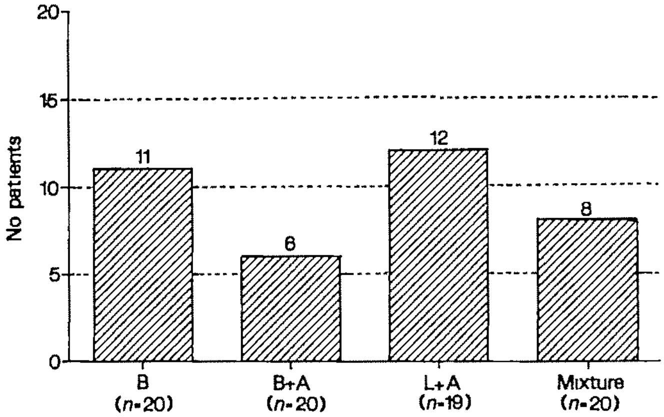

FIG. 1. Number of patients in each group requiring supplementary top-ups.

There was no difference between the four solutions in the time to provide adequate anaesthesia for surgery (mean onset time to surgical block 24.6 (SD 7.4) min): group B, 26.5 (SD 7.2) min; group B+A, 26.4 (SD 7.2) min; group L+A, 23.2 (SD 7.6) min and mixture, 22.4 (SD 6.6) min.

There were no excessively high blocks in any group, although four patients showed signs of sensory block up to C7 or C8 level. There was no difference between groups in terms of the maximum height achieved, and four patients had blocks up to T5 or T6.

TABLE I. *Number of patients in each group experiencing pain or discomfort during their Caesarean section.* *P < *0.05 compared with other groups*

	Bupivacaine	Bupivacaine +adrenaline	Lignocaine +adrenaline	Mixture
None	13	17	7*	15
Mild	2	2	9	4
Moderate	5	1	3	1
Severe	0	0	0	0

Surgery was possible in all patients under extradural anaesthesia, and none of the patients required or requested conversion to general anaesthesia. However, one patient in the lignocaine group had inadequate sensory block (patchy S1–T7) after 40 ml had been given, and surgery was possible only after an additional 10 ml of plain 0.5% bupivacaine. The results from this patient were therefore withdrawn from the study.

Sixty-six percent (52/79) of patients felt no pain at all. However, more pain was experienced by patients given lignocaine, as a significantly smaller number of patients in this group said they had had pain-free surgery ($P = 0.02$) (table I).

Although none of the patients described pain as severe, supplementary opioid analgesia was required by 13 patients (table II). Those in the lignocaine group required significantly more supplementary opioids than those given the other solutions ($P < 0.05$).

When the patients were asked how satisfactory they had found the extradural for their Caesarean section, 86% (68/79) stated it to have been

TABLE II. *Number of patients in each group requiring supplementary analgesia during Caesarean section.* *P < *0.05 compared with other groups*

	Bupivacaine ($n = 20$)	Bupivacaine +adrenaline ($n = 20$)	Lignocaine +adrenaline ($n = 19$)	Mixture ($n = 20$)
I.v. fentanyl	1	0	1	0
Extradural diamorphine	2	2	6	1
Entonox	0	0	0	1
Topical lignocaine	1	0	0	0
Total	4	2	7*	2

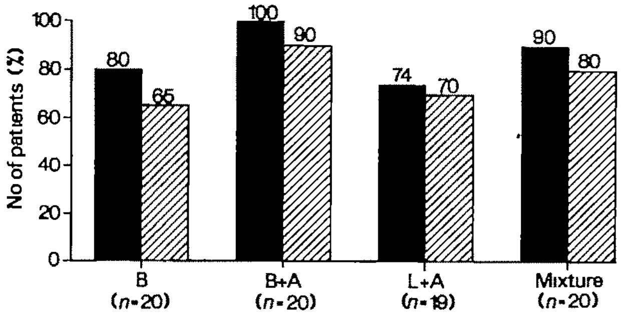

FIG. 2. Percent of patients (■) and anaesthetists (▨) who considered the quality of block produced by each solution was excellent or very good.

TABLE III. *Assessment by the patients and anaesthetists of the extradural block produced by the four local anaesthetic solutions. No significant difference between groups*

	Bupivacaine (*n* = 20)	Bupivacaine + adrenaline (*n* = 20)	Lignocaine + adrenaline (*n* = 20)	Mixture (*n* = 20)
Excellent	12 (10)	12 (15)	9 (10)	10 (10)
Very good	4 (3)	8 (3)	5 (4)	8 (6)
Good	2 (2)	0 (0)	3 (3)	2 (1)
Fair	1 (3)	0 (1)	2 (2)	0 (2)
Poor	1 (1)	0 (0)	0 (0)	0 (0)

excellent or very good (fig. 2). Only one patient considered her extradural to have been poor, and no significant difference was shown between the groups as assessed by either patients or anaesthetists. All 20 patients who received bupivacaine with adrenaline stated that the extradural was excellent or very good (table III). It is interesting to note, however, that the anaesthetists were uniformly unable to identify which of the four solutions was used.

There was no difference between groups in overall duration of sensory block. The mean time taken for the upper sensory level to regress by three segments measured in 12 patients in each group was 151 (SD 41) min (B: 152 (SD 35) min; B+A: 163 (SD 43) min; L+A: 135 (SD 41) min; mixture: 150 (SD 40) min). In addition, the duration of motor block was similar with all four solutions, with a mean duration of 195 (SD 75) min. More than 80% of patients in each group developed a motor block of Bromage grade 2 or 3.

Following the initial preload of crystalloid solution 1 litre, only five patients received no further fluids or ephedrine. In the remainder of the patients, an ephedrine infusion was used. The mean dose of ephedrine infused during the procedure was 29.1 (SD 19) mg, and there was no significant difference between the groups in the doses given (B: 35.4 (SD 20) mg; B+A: 23.0 (SD 10) mg; L+A: 30.0 (SD 23) mg; mixture: 28.0 (18) mg).

The pH of freshly prepared test solutions was measured on a Whatman PHA 250 apparatus, as was a commercial preparation of 0.5% bupivacaine with 1:200000 adrenaline (Astra Pharmaceuticals Ltd) (table IV).

All the babies delivered in this study were in good condition and had Apgar scores greater than 7 at 1 min and 9 or more at 5 min. None required resuscitation.

TABLE IV. *pH of samples of each extradural solution used compared with a commercial preparation as tested on a Whatman PHA 250 apparatus*

Extradural solution	pH
Bupivacaine	5.66
Bupivacaine + adrenaline	5.41
Lignocaine + adrenaline	4.81
Mixture	4.91
Commercial 0.5% bupivacaine + adrenaline (Astra Pharmaceuticals Ltd)	3.16

DISCUSSION

We found no difference in onset times between the agents used, and in particular lignocaine either alone or in the mixture did not work significantly faster than the bupivacaine solutions. With comparable solutions, our onset times are almost identical to those of Abboud and co-workers [6] and Laishley and Morgan [2], but faster than those in studies by Paech [8] and especially by Wilson and co-workers [3]. However, in the latter two studies, a slow incremental technique was used, and this would be expected to produce a block of slower onset. After performing a 3-ml test dose, we chose to give the whole of the 17-ml main dose as a slow continuous injection over 2 min. We consider this is safe, provided continuous observation of the patient is maintained during the injection. Inadvertent i.v injection should be detectable early by asking the patient to report unusual sensations during the slow injection itself. In addition, continuous ECG and automated arterial pressure recording are mandatory to provide objective warning of cardiovascular toxicity. We were ready to prevent hypotension by using an infusion of ephedrine after the initial 1-litre preload, as has been suggested by Datta and colleagues [9] and Yang, Abouleish and Caritis [10]. There has been much debate on the relative benefits of fluid infusion or vasoconstrictors, but the use of a vasoconstrictor such as ephedrine has been proposed recently as the most appropriate management [11].

Mixtures of bupivacaine and lignocaine have been used in non-obstetric situations with varied results. Magee, Sweet and Holland showed in surgical patients that the mixture produced sensory block of more rapid onset than that of bupivacaine alone [12]. However, Seow and colleagues found that, when solutions with adrenaline were used, the mixture produced marked motor block but there was no difference in onset times of sensory block compared with the individual agents [13]. We were unable to find any such differences in our obstetric patients.

Using a combination of chloroprocaine and bupivacaine for brachial plexus block, Cunningham and Kaplan found the time to maximum anaesthesia was halved compared with that of bupivacaine alone [14]. However, Cohen and Thurlow found no advantages in combining these two agents for extradural analgesia in labour [15]. To our knowledge, this is the only report of mixtures being used in obstetric patients.

In previous studies, the quality of the block produced by lignocaine with adrenaline was considered similar to that of bupivacaine, with or without adrenaline [8, 15]. However, we found that the block produced by lignocaine was substantially worse ($P < 0.05$) than that of all the other solutions tested, as more pain was experienced by the patients in this group, and more opioid supplementation was required. In addition, we had one seriously inadequate block which required supplementation with bupivacaine. Hence, contrary to the conclusions of Norton, Davies and Spicer [16], we found no advantage in the use of 2% lignocaine with adrenaline for Caesarean section, and indeed consider that it is unsuitable for this type of surgery. However, this should be distinguished from the use of 2% lignocaine with adrenaline to supplement a pre-existing bupivacaine extradural—an effective technique which is used commonly in this establishment.

Similar volumes of extradural solution were used in each group; this suggests that the four solutions were equipotent. The mixture worked as well as both bupivacaine solutions in providing good overall conditions for surgery, and both patient and anaesthetist satisfaction was high with this combination. The addition of bupivacaine to the lignocaine solution improved the quality of block produced. Although not statistically significant, there was a trend which suggested that bupivacaine with adrenaline performed best in almost every variable tested; it is possible that a follow-up study with larger groups would confirm this.

The pH values of the solutions used were considerably less than expected, although none was as low as that of the commercially prepared solution of bupivacaine with adrenaline. These are all much lower than the pK_a of bupivacaine or lignocaine, and this would result in a small proportion of the agents being present in the unionized form in solution. As this is the form which penetrates the nerve, and hence produces the effect, sub-optimal results may be expected. The adjustment of pH by adding sodium bicarbonate to each solution may have improved efficacy [17, 18].

The toxicity of local anaesthetics is reflected in the median convulsant dose, the CD_{50}, and the median lethal (cardiotoxic) dose, the LD_{50}. With bupivacaine, the safety window between these two values is small, in contrast with lignocaine, with which there is a wider difference [19]. Albright, amongst others, has pointed to the possible specific cardiotoxicity of bupivacaine compared with equipotent doses of other agents [7]. Reiz and Nath showed that bupivacaine was four times more potent than lignocaine in depressing myocardial contractility in pigs, but 16 times more potent in prolonging the QRS interval, which is a frequent antecedent of fatal ventricular fibrillation [20]. Interestingly, lignocaine has been used successfully in cats to treat bupivacaine-induced ventricular arrhythmias [21]. The toxicity of mixtures of amide local anaesthetics is poorly understood, and animal work suggests that it may be additive [19, 22]. However, De Jong and Bonin showed that the addition of lignocaine to bupivacaine widened the window between the CD_{50} and the LD_{50}, and concluded that convulsions from a bupivacaine–lignocaine mixture were less likely to terminate fatally than if bupivacaine were given alone [19].

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COMPARISON OF RINGER'S ACETATE WITH 3% DEXTRAN 70 FOR VOLUME LOADING BEFORE EXTRADURAL CAESAREAN SECTION

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SUMMARY

We have studied haemodilution and cardiovascular responses to i.v. hydration with either 3% dextran 70 (Dx70) or Ringer's acetate using a non-invasive cardiac output monitor (BoMed NCCOM3-R7) in 40 healthy parturients undergoing Caesarean section under extradural anaesthesia. Haemodilution was more pronounced, and central venous pressure, mean arterial pressure and cardiac index maintained at greater values, after treatment with Dx70. Colloid osmotic pressures (COP) decreased by 1.7 mm Hg after loading with 3% Dx70, and by 5.6 mm Hg in mothers treated with Ringer's acetate ($P < 0.001$). The transthoracic fluid index decreased more after hydration with Ringer's acetate ($P < 0.001$), indicating an increase in lung water. In spite of these maternal changes, there were no differences in neonatal bioimpedance or values of haemoglobin, PCV, albumin and COP in umbilical cord blood, and only one case of respiratory distress. We conclude that colloids may be preferable to crystalloids for circulatory preload for extradural Caesarean section, as greater haemodynamic stability was maintained and increases in lung water avoided.

KEY WORDS

Anaesthesia, obstetric: Caesarean section. Anaesthetic techniques: extradural Fluid balance: volume loading, colloid, crystalloid

An increased incidence of respiratory disturbances has been reported in full-term infants after Caesarean section (24% after elective operations compared with 5.5% after vaginal deliveries) [1]. One contributing factor to this may be the administration of fluids i.v. to prevent maternal hypotension during extradural or spinal anaesthesia. Maternal hypotension may cause fetal hypoxia, acidosis and neonatal depression [2–4], although other studies have failed to demonstrate neonatal acid–base disturbances following transient maternal hypotension [5, 6]. The ideal i.v. fluid for the parturient during regional anaesthesia should expand blood volume to maintain hydrostatic pressure in the uteroplacental vessels during sympathetic block, without passing into the fetal circulation. Although colloids may be theoretically preferable, particularly in view of an increase in interstitial lung water during pregnancy [7], in a recent study no adverse clinical effects were found with crystalloid volume loading [8].

We have studied the effects on the mother and fetus of crystalloid compared with colloid volume loading for extradural Caesarean section to examine this problem in greater detail.

PATIENTS AND METHODS

We studied healthy women ($n = 40$) without maternal or fetal complications undergoing primary or repeat Caesarean section at term. The study was approved by the Ethics Committee of Gothenburg University and all patients gave informed consent.

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Patients arrived unpremedicated in the surgical unit at 07:30. For measurements of central venous pressure (CVP) and blood sampling a "half-way" central venous catheter was inserted via the basilic vein as described by Ricksten and colleagues [9]. A peripheral vein was cannulated for administration of i.v. fluid. An extradural catheter was inserted via the L3–4 or L2–3 interspace.

Thoracic electrical bioimpedance measures the resistance of the thorax to a flow of high frequency, constant, low magnitude, alternating current. The thorax acts as a volume conductor. With each ventricular contraction the arterial vessel size changes, as do the alignment and velocity of red blood cells, resulting in changes in electrical conductance and a bioimpedance wave form. The NCCOM3-R7, BoMed (Medical Manufacturer, Ltd, Irvine, CA, U.S.A.) senses these bioimpedance changes accurately, thereby making possible continuous computerized measurements of cardiac index (CI) and stroke index (SI). In addition to this pulsatile component, measurement of thoracic electrical bioimpedance includes a steady state component which changes with thoracic fluid content. An increase in thoracic fluid volume reduces the thoracic fluid index (TFI) [10].

For measurement of thoracic electrical bioimpedance, eight electrodes were applied: two transmitting electrodes were placed bilaterally at the root of the neck and at the level of the xiphoid process in the midaxillary line. Two pairs of sensing electrodes were placed adjacent to the transmitting electrodes so that the centres of the electrodes were 5 cm apart. Basal haemodynamic data were recorded and blood samples obtained; subsequently an infusion of either 15 ml/kg body weight of Ringer's acetate (ionic composition (mmol litre^{-1}): Na^+ 130, K^+ 4, Ca^{2+} 2, Mg^{2+} 1, Cl^- 110, acetate 30) or 7.5 ml/kg body weight of 3% dextran 70 (Dx70) was given randomly over 20 min. The infusion of Dx70 was preceded by injection of 20 ml of monovalent hapten–dextran [11]. During this initial circulatory preload, bupivacaine 4–6 ml (5 mg ml^{-1}) was given extradurally with the patient in a semi-recumbent position. Thereafter, bupivacaine 14–24 ml was given extradurally in a supine position (with 15° left lateral tilt and 15° right lateral tilt for each half of the dose). Heart rate (HR) was monitored continuously during this procedure and maternal arterial pressure recorded every 2 min by an automatic non-invasive instrument (Hewlett Packard GmbH, model 78352 A, D-7030 Böblingen, Federal Republic of Germany). After institution of extradural anaesthesia, the same fluid loading was repeated over 30 min before the start of surgery. Thereafter Ringer's acetate 200 ml h^{-1} or Dx70 100 ml h^{-1} was given. Oxygen was administered via a face mask after induction of extradural anaesthesia.

The infusion rate was increased if systolic arterial pressure (SAP) decreased to less than 100 mm Hg and, below 95 mm Hg, ephedrine 10 mg was given i.v. Values of thoracic electrical impedance and CVP were recorded semi-continuously throughout the procedure. Blood sampling was performed repeatedly for measurement of haemoglobin, albumin, protein, sodium, potassium and glucose concentrations and activated partial thromboplastin time (APTT), prothrombin time, osmolality and PCV. Analyses were performed according to routine laboratory practice. Colloid osmotic pressure (COP) was measured on plasma samples using a Tybjaerg Hansen type of colloid osmometer modified for small fluid samples [12].

Time from uterine incision to delivery was recorded. Apgar scores at 1 and 5 min were assessed. At birth, blood was sampled from the umbilical cord for measurement of haemoglobin, PCV, albumin content and COP. The babies' ventilatory frequencies and heart rates were measured and they were studied also with transthoracic electrical bioimpedance to assess change in impedance from 30 to 120 min after delivery (impedance monitor, Department of Medical Electronics, Chalmer's University of Technology, Gothenburg).

Student's *t* test, linear regression and Fisher's exact test were used for statistical analysis. Values are given as mean (SE). $P \leqslant 0.05$ was considered significant.

RESULTS

There were no differences between the patients in the Ringer's acetate and Dx70 groups except for the sex distribution of the neonates (table I). All patients had satisfactory anaesthesia and did not require supplementary anaesthetic before delivery (anaesthetic level, as assessed by skin temperature: T4.7 (0.2) with 25.7 (1.0) ml of bupivacaine 5 mg ml^{-1} in the Ringer's acetate group and T4.8 (0.2) with 26.8 (1.0) ml in the Dx70 group). Midazolam 1 mg, offered to all patients after parturition, was given to three of the Dx70 group

TABLE I. *Maternal and neonatal characteristics (mean* (SD))

	Ringer's acetate ($n = 20$)	3% Dextran 70 ($n = 20$)	P
Age (yr)	31 (4)	30 (5)	ns
Height (cm)	163 (8)	164 (7)	ns
Weight (kg)	72.5 (10.9)	71.2 (9.3)	ns
SAP (mm Hg)	127 (13)	128 (10)	ns
DAP (mm Hg)	72 (10)	73 (9)	ns
Gestational age (week)	38.1 (0.7)	38.2 (0.7)	ns
Birth weight (g)	3446 (534)	3486 (291)	ns
Sex (M/F)	8/12	15/5	< 0.05

TABLE II. *Maternal blood chemistry (mean* (SD)). *n = 20 each sampling. RA = Ringer's acetate; Dx70 = 3% dextran 70; COP = colloid osmotic pressure.* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; *dextran* vs *Ringer's acetate solution (unpaired* t *test)*

	Before loading	After 1st loading	After 2nd loading	Postpartum	
				0.5 h	3 h
Haemoglobin (g litre^{-1})					
RA	124 (7)	114 (10)	112 (6)	115 (6)	119 (7)
Dx70	122 (8)	111 (7)	104 (6)***	107 (8)***	109 (9)
PCV (%)					
RA	37 (3)	33 (3)	33 (2)	34 (2)	35 (3)
Dx70	37 (3)	33 (3)	31 (2)**	32 (3)**	33 (3)*
Serum protein (g litre^{-1})					
RA	58 (3)	50 (4)	49 (3)	50 (3)	51 (4)
Dx70	60 (2)*	53 (3)*	48 (3)	47 (3)**	47 (3)**
Serum albumin (g litre^{-1})					
RA	33 (3)	28 (2)	28 (3)	28 (3)	28 (2)
Dx70	32 (2)	28 (2)*	26 (2)**	26 (2)**	25 (2)***
Plasma COP (mm Hg)					
RA	23.1 (2.4)		17.5 (2.2)		22.1 (2.0)
Dx70	22.9 (2.7)		21.2 (2.9)***		25.3 (2.3)***

and eight of the Ringer's acetate group. Fentanyl 0.05 mg was given to two patients in each group.

The concentrations of haemoglobin, albumin and protein, and PCV were reduced significantly ($P < 0.001$) in response to the first fluid loading in both groups (table II). Further haemodilution during the second fluid loading occurred only in the Dx70-treated patients. Haemodilution calculated from haemoglobin and PCV values was about 5% in Ringer's acetate-treated patients and about 10% in the Dx70 patients 3 h after delivery. The estimated peroperative blood loss was similar in both groups (428 (50) ml in the Ringer's acetate group and 361 (42) ml in the Dx70 group), and calculated as about 7% of blood volume. Osmolality, APTT, prothrombin time, and sodium, potassium and glucose concentrations were within the normal range and remained largely unchanged throughout the study in both groups and are, therefore, not included in table II. COP was significantly greater in Dx70-treated mothers immediately before parturition and at 3 h after parturition (table II) compared with mothers in whom volume loading was with Ringer's acetate ($P < 0.001$). At maximum haemodilution immediately before parturition, 12 of 19 mothers given Ringer's acetate and two of 20 given Dx70 had COP values of $\leqslant$ 17.5 mm Hg (fig. 1).

One patient in the Ringer's acetate group and two patients in the Dx70 group developed hypotension before extradural anaesthesia. This was relieved by exaggerating the left lateral tilt. Hypotension (SAP less than 100 mm Hg) occurred 10–20 min after the main dose of extradural anaesthetic in five patients given Ringer's acetate (two to 90–99 mm Hg, two to 80–89 mm Hg and one to 70 mm Hg) and in one patient given Dx70 (90–99 mm Hg). Ephedrine

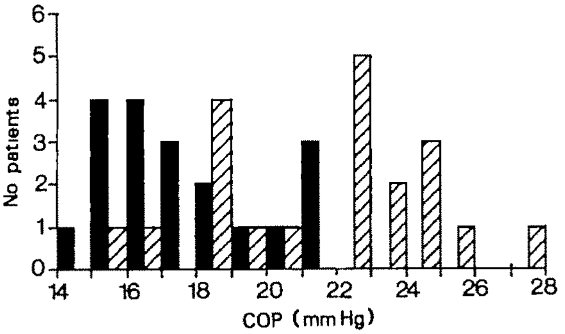

FIG. 1. Distribution of COP values immediately before parturition in patients treated with RA (■) or Dx70 (▨).

was effective immediately in treatment of hypotension in all these patients. Mean arterial pressure (MAP) was greater in the Dx70 group (fig. 2). SI increased in both groups during fluid loading and remained increased in the postoperative phase in Dx70 patients. HR was also slightly greater in Dx70 patients, as was CI (fig. 2). Calculated systemic vascular resistance index (SVRI) decreased in response to sympathetic block similarly in all patients (fig. 2).

CVP increased similarly and only in response to the second fluid loading in both groups, but decreased more rapidly after parturition in Ringer's acetate-treated patients (fig. 3). Decrease in TFI, indicative of thoracic fluid accumulation, was more pronounced after Ringer's acetate than after Dx70 (fig. 3), but there was no significant correlation between maternal changes in COP and TFI.

Urinary output was greater after Ringer's acetate (total 858 (91) ml 3 h after parturition) than after Dx70 treatment (430 (60) ml).

The uterine incision to delivery time was 38.5 (3.6) s in the Ringer's acetate group and 49.2 (3.6) s in the Dx70 group ($P < 0.05$). Apgar scores were 9 or 10 at 1 and 5 min in all babies. One neonate (Dx70 group) developed a transient mild respiratory disturbance with tachypnoea and required oxygen (up to 30%) for 24 h. All other babies were healthy. No difference in haemoglobin and albumin concentrations or PCV occurred in umbilical cord blood between the two fluid regimens (table III), but there were wide individual differences. The mean change in impedance was +0.5 (SD 2.0) ohm in babies whose

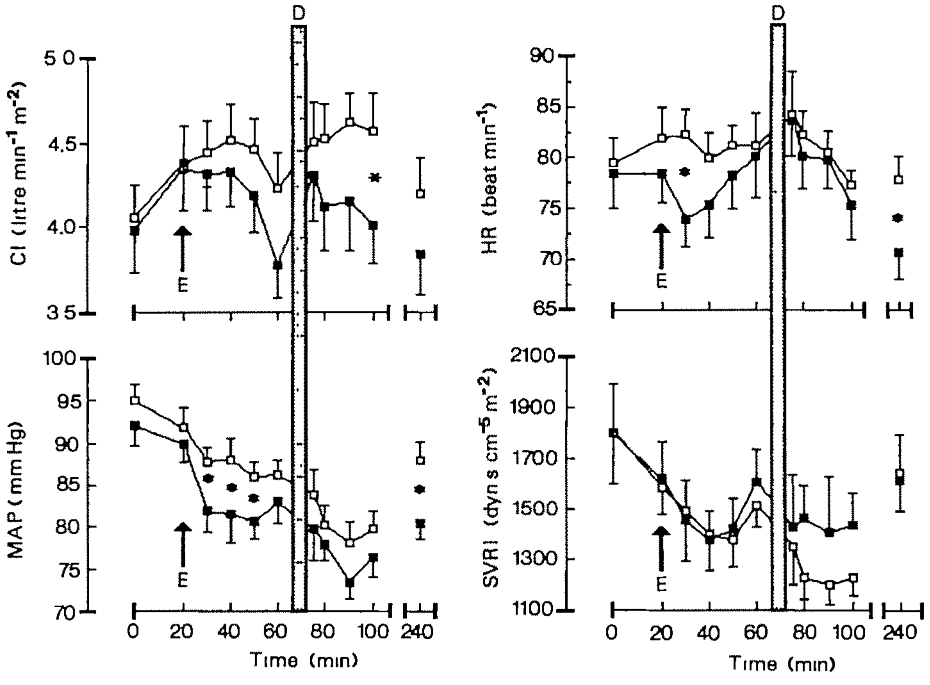

FIG. 2. Cardiac index (CI), mean arterial pressure (MAP), heart rate (HR) and systemic vascular resistance index (SVRI). E = Main dose of extradural anaesthetic; D = delivery. Mean values, SE. ■ = Ringer's acetate; □ = Dx70. $*P \leqslant 0.05$; Ringer's acetate *vs* Dx70.

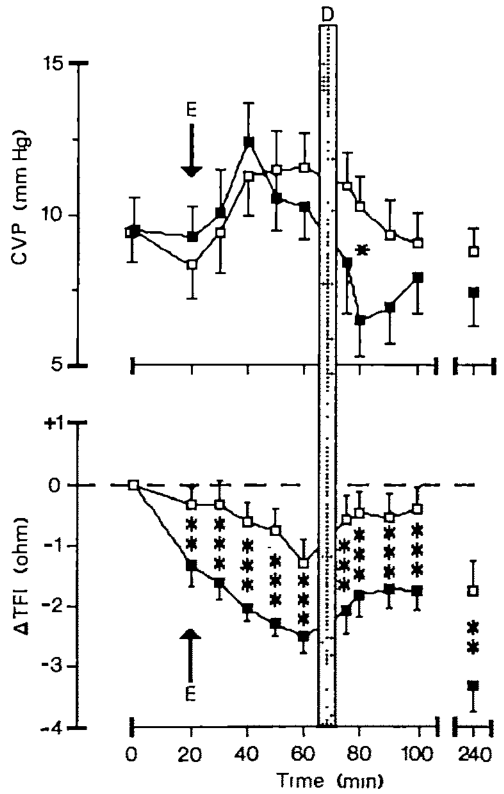

FIG. 3. Central venous pressure (CVP) and changes in thoracic fluid index. E = Main dose of extradural anaesthetic; D = delivery. Mean values, SE. ■ = Ringer's acetate; □ = Dx70. $*P \leqslant 0.05$; $**P \leqslant 0.01$; $***P \leqslant 0.001$; Ringer's acetate *vs* Dx70

mother had received Ringer's acetate, while babies of Dx70-treated mothers showed a mean change in impedance of −0.2 (SD 2.1) ohm. This difference was not significant. COP did not differ between the two groups of infants (table III), in spite of the significant maternal difference.

DISCUSSION

There are several reports of fetal bradycardia, asphyxia, acidosis and neurological depression in the newborn in response to maternal hypotension during regional anaesthetic techniques [2–4], but the neonate does not seem to be harmed by extradural anaesthesia if maternal hypotension is treated rapidly. The duration of hypotension may be more important than its severity [5, 6].

In the present study, maternal hypotension was minimized by 15° left lateral tilt, which seemed adequate to prevent caval compression, as CVP was relatively high before delivery in both groups. Caval compression caused by the supine position has been shown to induce fetal acidosis and accumulation of bupivacaine in the newborn [3]. The volumes of crystalloid or colloid solution used in the present study may seem large, but similar volumes have been reported previously to be optimal in controlling maternal hypotension during extradural anaesthesia [14–16]. In the present study, an overall incidence of only 15 % of maternal hypotension occurred; hypotension was treated immediately and this may have been beneficial for the neonate. An incidence of 10 cases of respiratory disturbances may have been expected statistically [1], but only one case of respiratory distress occurred.

Maternal haemodynamic state was assessed using a computerized thoracic electrical impedance monitor. The NCCOM3-R7 equipment [10] has been shown to be as accurate as thermodilution for measurement of cardiac output in most situations, including the peripartum period [17, 18]. The haemodynamic and laboratory data indicate that volume expansion was more pronounced and prolonged with Dx70 than with Ringer's acetate. No adverse reactions (no signs of cardiac decompensation or postpartum hypertension) were observed from hypervolaemia after infusion of Dx70 to the mothers.

The change in TFI was more pronounced after infusion of Ringer's acetate, indicating that thoracic fluid content was increased in these mothers. It has been reported recently that bioelectrical impedance is a useful technique for measurement of extracellular fluid volume and that the invasive

TABLE III. *Umbilical cord blood chemistry (mean (SD)). COP = Colloid osmotic pressure. No significant differences between groups*

	Ringer's acetate	3% Dextran 70
Haemoglobin (g litre^{-1})	156 (18) (n = 14)	153 (22) (n = 14)
PCV (%)	47 (5) (n = 12)	44 (7) (n = 12)
Serum albumin (g litre^{-1})	35 (3) (n = 16)	34 (2) (n = 13)
Plasma COP (mm Hg)	21.3 (2.4) (n = 15)	21.6 (2.1) (n = 14)

sodium bromide method correlates well with bioimpedance [19]. Bioimpedance has been found also to correlate with the double dye dilution technique for measurement of extravascular lung water [20]. Thus TFI measures extracellular thoracic fluid (intravascular and interstitial). The thoracic intravascular volume may have been slightly larger in the Dx70 patients according to calculations of haemodilution, in spite of absence of major differences in CVP. Consequently, the reduction in TFI (increased conductivity) after Ringer's acetate treatment probably represents an increase in extravascular lung water. It is surprising to find such a pronounced increase in response to the decrease in COP, as no significant increase in extravascular lung water was observed in patients undergoing reconstructive aortic surgery following a similar reduction of COP [21]. However, positive pressure ventilation was used in that study. In addition, there seems to be a considerable increase in lung water in women at term measurable even with radiological methods, and this is not caused entirely by dilated pulmonary vessels [7]. The present results suggest, therefore, that increased pulmonary hydration or even oedema may occur if excessive volumes of crystalloids are used for volume loading for Caesarean section.

No adverse effects on fetal PCV, albumin concentration, COP or neonatal respiration were observed with either fluid regimen. There was a smaller overall incidence of neonatal respiratory distress than expected. Thus the original hypothesis that a colloid would be restricted to the maternal circulation and therefore more favourable for the fetus could not be substantiated. However, surgery always started 30–40 min after institution of extradural anaesthesia and if a longer period had elapsed, the reduction in maternal COP might have been reflected in umbilical cord blood.

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PHARMACOKINETICS OF PROPOFOL IN CHILDREN

R. D. M. JONES, K. CHAN AND L. J. ANDREW

SUMMARY

The pharmacokinetics of propofol were studied in 12 healthy Chinese children, aged 4–12 yr, undergoing circumcision under inhalation anaesthesia. All patients received a single i.v. bolus dose of propofol 2.5 mg kg^{-1} and blood concentrations of propofol over the subsequent 24 h were measured using high pressure liquid chromatography with fluorimetric detection. Data were consistent with a three-compartment model with a mean (SEM) elimination half-life of 209 (29) min and total body clearance of 40.4 (3.6) ml min^{-1} kg^{-1}. The mean (SEM) apparent volume of distribution at steady state was 5.0 (2.7) litre kg^{-1} and volume of the central compartment was 0.6 (0.1) litre kg^{-1}. The mean (SEM) ratio of k_{12}:k_{21} was 1.4 (0.2), suggesting that, after injection of a single bolus dose in children, propofol is distributed rapidly to the shallow compartment. The mean ratio of k_{31}:k_{10} suggests that lipophilicity constrains return of the drug to the central compartment.

KEY WORDS

Anaesthetics, intravenous. propofol. Anaesthesia: paediatric. Pharmacokinetics propofol, children.

Rapid recovery after general anaesthesia may be an advantage in paediatric patients, particularly those undergoing minor day-care surgery. Propofol seems to confer some advantage over other available agents in this respect [1]. The pharmacology of propofol has been reviewed by White [2] but, although there has been a rapid accumulation of clinical and pharmacological data, there have been few reports on the pharmacokinetics of propofol in children [3, 4].

Age-related changes in body water, lean body mass, regional blood flow, renal and hepatic function [5–7] affect drug distribution, metabolism and excretion [8–10]. We report the first phase of a series of studies investigating the pharmacokinetics of propofol in Chinese children.

PATIENTS AND METHODS

Twelve Chinese children, aged 4–12 yr, were studied. All patients were ASA grade I and underwent circumcision for the treatment of phimosis. The study was approved by the Faculty of Medicine Ethics Committee (University of Hong Kong) and written, informed consent was obtained from the parents. Children were excluded from the study if there was a history of asthma or allergies, previous adverse anaesthetic experience, halothane anaesthesia within the previous month, hepatic, renal, respiratory, cardiac or haematological disease, mental retardation and age less than 2 yr.

Patients were premedicated with trimeprazine 3 mg kg^{-1} (maximum 90 mg) and atropine 0.03 mg kg^{-1} by mouth 2 h before operation. EMLA emulsion cream 2 g (lignocaine 25 mg g^{-1} and prilocaine 25 mg g^{-1}) was applied also to the dorsum of the left hand. In the operating suite, a 24-gauge cannula was inserted into a vein underlying the EMLA-pretreated area. Procaine hydrochloride 1 mg kg^{-1} was administered 15 s before induction of anaesthesia with the aqueous emulsion formulation of propofol (Diprivan) 2.5 mg kg^{-1} injected over 30 s. Time zero was taken at completion of the injection. An 18-gauge cannula was inserted into a vein in the contralateral antecubital fossa for venous sampling. Thereafter, anaesthesia was maintained with the patient breathing spontaneously 67% nitrous

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oxide and 1–3% halothane in oxygen via a Mapleson F (< 25 kg) or a Mapleson A (> 25 kg) breathing system. The surgeon infiltrated each dorsal nerve at the root of the penis with 0.5% bupivacaine 1.5 ml.

On arrival in the operating suite the children were assessed and recorded as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command [11]. Induction was graded as good (absence of side effects), adequate (side effects present but not interfering with induction) and poor (side effects severe and protracted). Evidence of excitatory phenomena on induction of anaesthesia was recorded also. During anaesthesia, all patients were monitored with an electrocardiograph, non-invasive arterial pressure cuff, pulse oximeter, capnograph and for inspired oxygen concentration (Datex, Cardiocap). After operation, the patient's coma scale [12] and a structured observation score [13] were assessed and noted at each of the blood sampling times. The awakening time (time from the discontinuation of general anaesthesia to spontaneous eye-opening) and time until the patient could identify himself were recorded also.

Samples were collected for measurement of whole blood concentration of propofol at 2, 5, 10, 15, 20, 30, 45, 60, 90, 120 and 180 min and 4, 6, 8, 10, 12, 18 and 24 h. Each sample was mixed thoroughly in tubes containing lithium–heparin (Sarstedt LH/5) and stored at +4 °C until assayed. Propofol concentrations in whole blood were determined by a modified liquid chromatography method [14]. Propofol in whole blood (0.5-ml samples rather than 1.0-ml samples used by Plummer [15]) and internal standard thymol, buffered with sodium dihydrogen phosphate 0.1 mol litre^{-1}, were extracted into cyclohexane. The mobile phase consisted of 75% (v/v) acetonitrile in distilled water containing 1% (v/v) glacial acetic acid. A C_{18} reversed phase column (Nova-Pak), linked to a C_{18} pre-column was used and the eluate was measured by a fluorimetric detector with excitation and emission wavelengths set at 276 nm and 310 nm, respectively [16]. The calibration graphs were linear over the range 2–3000 ng ml^{-1} with coefficients of variation ranging from 1.0 to 8.0%. The between-batch coefficient of variance was 6.7% at 50 ng ml^{-1} and 4.8% at 3000 ng ml^{-1}. The limit of detection was approximately 2 ng ml^{-1}.

Blood concentration–time profiles of propofol were analysed by the BITRI computer program [14, 17] which utilizes the method of residuals, whereby each curve is fitted with experimental data in terms of a bi-exponential or tri-exponential function. BITRI chooses the best fit such that the logarithms of squared deviation between exponential and computer values are minimized [18].

Distribution and elimination half-lives ($T_{\frac{1}{2}}^{\alpha}$ $T_{\frac{1}{2}}^{\beta}$ $T_{\frac{1}{2}}^{\gamma}$), apparent central volume of distribution (V), apparent volume of distribution at steady state (V^{ss}), apparent volume of distribution in the elimination phase (V^{γ}) and total body clearance (Cl) were calculated using standard formulae [19].

RESULTS

On arrival in the operating suite, two of the children were awake and apparently anxiety free, seven patients were drowsy with intermittent eye opening and the remaining three children were asleep but awoke on command. Induction of anaesthesia was devoid of side effects in 50% of patients and satisfactory in the remainder. Five episodes of semi-purposeful movement occurred, combined with breath-holding, tremor and rigidity in two patients, and one patient developed hiccup.

The demographic and haemodynamic changes during induction and details of anaesthesia are shown in table I. The maximum change in heart rate and systolic arterial pressure from pre-induction values during the first 5 min of the induction period was calculated. The mean maximum end-tidal carbon dioxide value recorded

TABLE I. *Demographic, induction haemodynamics and anaesthetic data in the 12 children (mean (SEM) [range])*

Age (yr)	7.9 (0.8)	[4–12]
Weight (kg)	25.8 (7.9)	[16–39]
Mean increase in heart rate from pre-induction values (beat min^{-1})	4.3 (6.4)	[−42 to +42]
Mean decrease in systolic arterial pressure from pre-induction values (mm Hg)	−7.1 (4.4)	[−28 to +16]
Maximal end-tidal carbon dioxide recorded during anaesthesia (kPa)	6.8 (0.3)	[5.3–7.8]
Anaesthesia time (min)	28.8 (1.5)	[21–36]
Awakening time (min)	30.5 (4.0)	[11–61]

TABLE II. *Relationship between awakening, as assessed by coma score [10], and time after induction dose of propofol. (Mean* (SEM) *anaesthesia time 30.5 (5.13) min)*

	Time after induction (min)				
	< 45	45–60	60–90	90–120	120–240
Coma score 7 Lightly asleep, eyes open on command (n = 11)	1	9	0	1	0
Coma score 9 Fully awake, eyes open, conversing (n = 11)	0	3	2	4	2

during surgery was 6.8 kPa, and mean anaesthetic time was 28.8 min. Mean awakening time was 30.5 min; awakening occurred at a mean blood concentration of propofol 165 ng ml^{-1}. In all cases, the children could identify themselves adequately within 2 min of opening their eyes spontaneously. Coma scores are shown in table II.

Mean blood concentrations of propofol declined in all patients but secondary peaks were present at 3 and 12 h (fig. 1). Propofol concentrations were detectable in only five patients at 10 h and only two patients at 24 h. In all patients, compartmental analysis of propofol concentrations revealed a three-compartment model with elimination from a central compartment. The pharmacokinetic findings are summarized in table III. The mean (SEM) ratio of $k_{12}:k_{21}$ was 1.435

TABLE III. *Pharmacokinetic findings in the 12 children. Volumes of distribution at steady state* V^{ss} *and equilibrium* (V^{γ}), *volume of central compartment* (V), *total body clearance* (Cl), *half-lives of the three phases* ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$, $T_{\frac{1}{2}}^{\gamma}$) *and rate constants (mean* (SEM) *[range])*

V^{ss} (litre)	133.34 (25.56)	[20.25–345.40]
(litre kg^{-1})	5.01 (2.66)	[1.68–10.16]
V^{γ} (litre)	325.47 (61.22)	[44.63–570.11]
(litre kg^{-1})	12.38 (1.98)	[2.23–23.50]
V (litre)	16.31 (3.77)	[2.45–41.94]
(litre kg^{-1})	0.597 (0.10)	[0.08–1.23]
Cl (litre min^{-1})	1.11 (0.18)	[0.53–1.43]
(ml min^{-1} kg^{-1})	40.35 (3.60)	[25.70–66.75]
$T_{\frac{1}{2}}^{\alpha}$ (min)	3.05 (0.43)	[1.01–6.44]
$T_{\frac{1}{2}}^{\beta}$ (min)	24.33 (5.13)	[5.26–74.99]
$T_{\frac{1}{2}}^{\gamma}$ (min)	209.22 (29.26)	[37.88–285.97]
k_{31} (h^{-1})	0.55 (0.22)	[0.18–2.97]
k_{10} (h^{-1})	6.40 (1.52)	[1.81–19.55]
k_{13} (h^{-1})	2.84 (0.72)	[0.64–9.47]
k_{12} (h^{-1})	5.79 (1.11)	[0.31–11.98]
k_{21} (h^{-1})	4.85 (0.82)	[1.31–9.96]
$k_{31}:k_{10}$	0.169 (0.074)	[0.02–0.89]
$k_{12}:k_{21}$	1.435 (0.224)	[0.03–2.58]

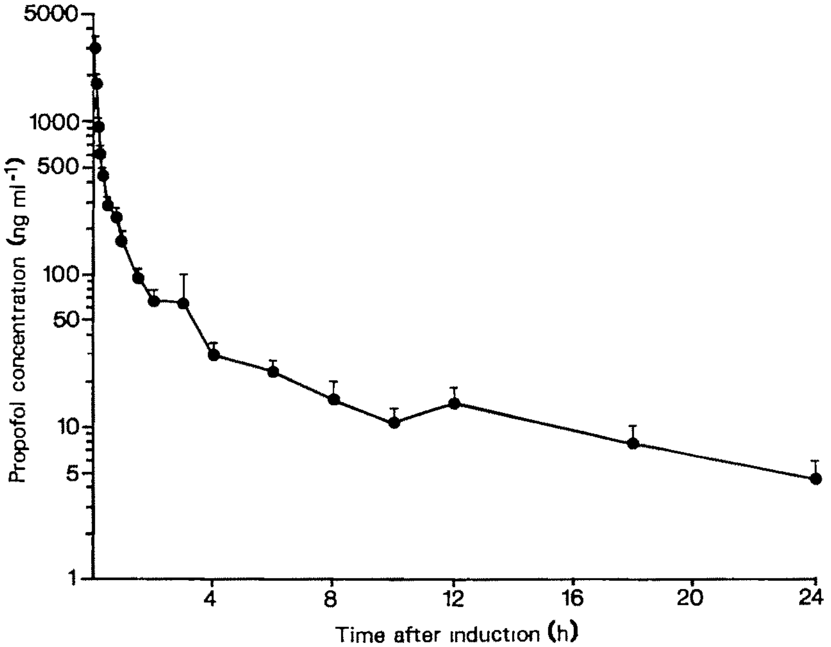

FIG. 1. Mean (SEM) blood propofol concentrations.

(0.224), suggesting a rapid distribution of the i.v. propofol bolus to the shallow compartment, and the mean ratio of $k_{31}:k_{10}$ was 0.1692 (0.074), suggesting that the third exponential phase was constrained by its slow return from the deep to the central compartment. Linear regression demonstrated a significant increase in the rate of elimination of propofol with increasing age ($P <$ 0.001) (fig. 2). However, there was no significant relationship between clearance of propofol and age (fig. 3) [20]. No relationship was found between age and V^{ss}, V or V^{γ} with linear regression analysis.

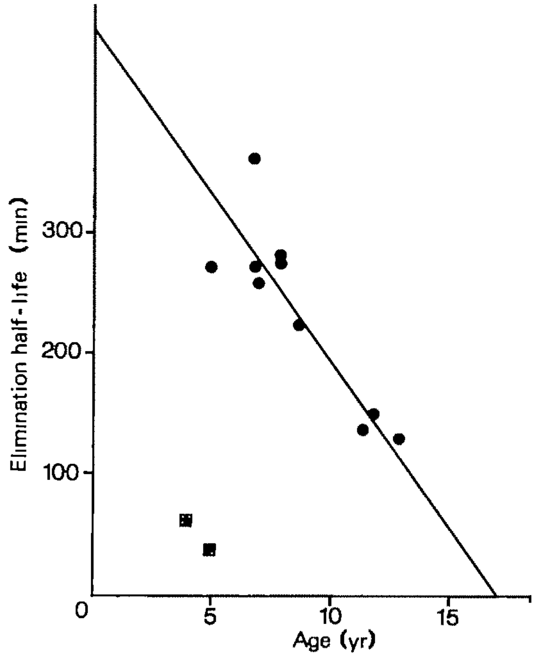

FIG. 2. Relationship between age and elimination half-life. The two outlying data points enclosed in the boxes were excluded from linear regression analysis. $r = 0.73$; $P < 0.001$.

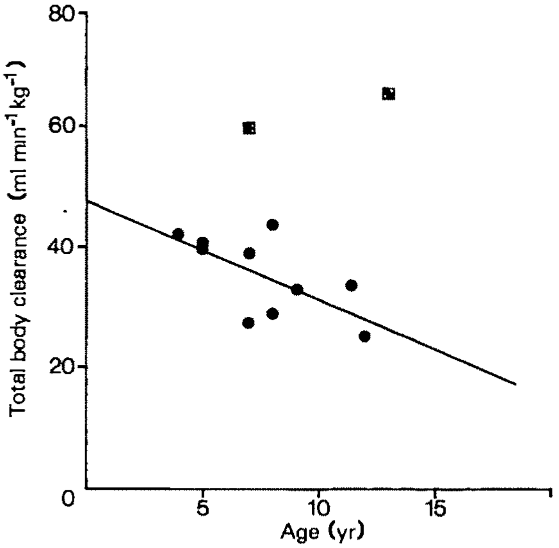

FIG. 3. Relationship between age and clearance. The two outlying data points enclosed in the boxes were excluded from linear regression analysis. $r = 0.41$; $P = 0.046$.

Anaesthesia and recovery proceeded smoothly in all patients and there were no complications.

DISCUSSION

Pharmacokinetic studies in children are often restricted by the limited amount of blood that can be removed from the patient, a consequence of which is a lack of definition of the elimination phase. In this study, blood concentrations of propofol in 12 children have been determined using small volume samples for up to 24 h after induction. In all these children, the clearance of propofol from the blood may be described best by a tri-exponential function. The pharmacokinetic data show a mean $T_{\frac{1}{2}}^{\gamma}$ of 209 min and mean Cl of 1.11 litre min^{-1}. This large total body clearance combined with a relatively small mean volume of distribution at equilibrium (325.5 litre) for a highly lipophilic drug, results in a fast elimination of propofol from the blood in children. As in another study in young adults [21], mean volume of distribution at steady-state was less than 50 % of the mean equilibrium volume of distribution. This suggests that, after distribution from the blood to the tissue and metabolic clearance from the blood, elimination is constrained by a slow return of propofol to the blood from the deep compartment.

The pharmacokinetic findings of Valtonen and colleagues [3] and Saint-Maurice and colleagues [4] are summarized in table IV and compared with the data from this study. The initial distribution half-life determined in our study and that of Saint-Maurice are similar, perhaps reflecting the similar sampling times. The SD of Valtonen's data is equal to their mean $T_{\frac{1}{2}}^{\alpha}$. The elimination half-life, central compartment volume and plasma clearance values from Valtonen's study and our's are similar. V^{ss} in Saint-Maurice's study is twice our value and five times that of Valtonen's data, and the elimination half-life determined by Saint-Maurice's group was three times as long. The differences between these studies may be at-

TABLE IV. *Comparison of three pharmacokinetic studies of single dose propofol in children*

	Valtonen [3] ($n = 8$) Mean (SD)	Saint-Maurice [4] ($n = 8+2$ for 4 h) Mean (SEM)	Present study ($n = 12$) Mean (SEM)
$T_{\frac{1}{2}}^{\alpha}$ (min)	1.50 (1.56)	4.15 (0.78)	3.05 (0 43)
$T_{\frac{1}{2}}^{\beta}$ (min)	9.3 (3.78)	56.1 (6.30)	24.3 (5.13)
$T_{\frac{1}{2}}^{\gamma}$ min	214.6 (168.8)	735.0 (82.7)	209.22 (29.3)
V (litre kg^{-1})	0.530 (0.65)	0.722 (0.11)	0.597 (0 10)
V^{ss} (litre kg^{-1})	2.16 (1.49)	10.90 (1.20)	5.01 (2.66)
Cl (ml min^{-1} kg^{-1})	32.0 (16.8)	30.6 (2.9)	40.4 (3.6)
Sampling times (min)	2, 4, 6, 10, 15, 30, 45, 60	2, 5, 10, 15, 20, 30, 45, 60, 90, 120	2, 5, 10, 15, 20, 30, 45, 60, 90, 120
(h)	3, 6, 12, 24	3, 4, 5, 6, 7, 8, 10, 12, 24	3, 4, 6, 8, 10, 12, 18, 24
Surgery	"Elective surgery"	Minor visceral Minor orthopaedic	Circumcision
Drugs given	Atropine Flunitrazepam Lignocaine		Atropine Trimeprazine Procaine HCl
	Fentanyl Pancuronium Suxamethonium	Fentanyl Vecuronium	
		Halothane ($n = 9$) Enflurane ($n = 1$)	Halothane
	O_2:N_2O	O_2:N_2O	O_2:N_2O Caudal bupivacaine

tributable to the different anaesthetic techniques used, different types of surgical procedure, different sample collection times and the small populations examined. The smaller lean body mass of Chinese children may decrease V^{ss}, leading to a shorter elimination half-life. Similar results have been found with the pharmacokinetics of diazepam in Chinese adults [22]. The influence of ethnic origin on metabolism may contribute to these differences also, as it does, for example, with the increased oxidative demethylation of pethidine in Oriental subjects [23]. The present study was performed with a standardized anaesthetic technique, the same simple surgical procedure in all cases and 24-h sampling in 12 patients.

Despite the small population sample, and the exclusion of two outlying points from the linear regression analysis, the decrease in elimination half-life with increasing age was statistically significant (fig. 2). Each of the outlying points belongs to a different patient and does not show any relation to the clinical or blood analysis data. The only constant feature of this sub-group of patients was that propofol could not be detected in blood samples after the 10-h post-induction blood sample. Blood samples were assayed randomly, standardized pre- and post-batch, and collected in the same manner by the same investigator throughout the study. It is likely that, in this group of young children, metabolizing capacity is developing rapidly, and this is reflected by the inverse relationship of elimination half-life and age. Propofol is metabolized rapidly to the inactive glucuronide conjugate and the corresponding quinol glucuronide. Not only is glucuronidation an age-dependent enzyme process, but both hepatic mass and hepatic blood flow increase towards adulthood [24]. Two children, aged 7 yr, who took the longest to awaken fully were included in the elimination–age regression data ($T_{\frac{1}{2}}^{\gamma}$ 262 and 276 min). Unfortunately, the recovery data are confounded by the long half-life of the premedicant trimeprazine. Nevertheless, 91% of children had awoken within 30 min of termination of anaesthesia and could be returned from the recovery area to the ward. With our anaesthetic technique, awakening occurred at approximately twice the $T_{\frac{1}{2}}^{\beta}$ with a mean blood concentration of 165 ng ml^{-1}. There are no comparable data in the literature but adults, premedicated with hydroxyzine [25] or promethazine [26], had mean recovery times (22 and 16.3 min, respectively) approximately double those of unpremedicated adults.

Both our study and that of Valtonen and colleagues [3] demonstrated a tri-exponential relationship between blood concentrations and time. The data from two patients in the study of Saint-Maurice and colleagues [4] were not available after 4 h and their pharmacokinetic variable estimates for these patients were based on a two-compartment open mamillary model. However, it is possible to make a comparison of propofol half-lives between non-pregnant adults and children [27–29], although interpretation should be prudent in view of the varying anaesthetic techniques. The present study in children demonstrated a $T_{\frac{1}{2}}^{\alpha}$ similar to that in adults. Estimation of the initial distribution half-life of propofol is liable to error in the present study because our first sample was drawn at 2 min after induction. However, it was shown that, when blood sampling at 2, 4, 6, 8 and 10 min after induction with propofol in women undergoing laparoscopy was compared with sampling at 2, 5, 10 and 15 min in women undergoing Caesarean section, there were no significant pharmacokinetic differences [14]. The $T_{\frac{1}{2}}^{\beta}$ of our children was approximately 50 % and elimination half-life 33 % of the duration of those of the young adults in the study by Kirkpatrick and colleagues [21]. Only two patients in our study had detectable concentrations of propofol at 24 h. This may imply that our children had rapid metabolic elimination of the drug. The volume of the central compartment, when normalized for body weight, did not differ significantly from the young adults, but V^{ss} was approximately 50 %. This may reflect the proportionately larger lipid content of the Caucasian adult compared with the Chinese child.

The rapid hepatic clearance of a highly protein-bound drug such as propofol [29] is limited primarily by hepatic blood flow. Halothane reduces hepatic blood flow and may inhibit liver enzymes [7]. However, in the series of Brigg and colleagues, the propofol concentrations in a group of patients whose anaesthesia included halothane were not significantly different from those in other groups [27]. In our study, the recorded haemodynamic changes on induction were minimal.

In conclusion, we have observed that the pharmacokinetics of propofol in children are similar to those in adults and are consistent with a three-compartment model with elimination from a central compartment. The elimination half-life of propofol in children is similar to that reported with a bolus i.v administration of methohexitone in paediatric patients [7] and approximately 30 % that reported with thiopentone [30]. The rapid elimination of propofol and minimal haemodynamic changes during induction qualify this agent as suitable for use in induction of anaesthesia in children.

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PHARMACOKINETICS OF ATRACURIUM DURING CONTINUOUS INFUSION

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SUMMARY

The pharmacokinetics of atracurium were investigated by a model-independent method during continuous infusion under propofol anaesthesia. Following an intubating dose of suxamethonium, atracurium was infused according to a predetermined profile which continually set the infusion rate to maintain stable muscle paralysis and a target steady state plasma concentration when equilibrium between the biophase and plasma had occurred. Atracurium was infused for the first 1 h to maintain a target steady state plasma concentration of 1.0 µg ml^{-1}. Thereafter, the target plasma concentration was adjusted to maintain 90% muscle paralysis. The maintenance infusion rate required to maintain 90% paralysis was 4.25 (SD) 1.11 µg kg^{-1} min^{-1}, with an estimated steady state plasma concentration of atracurium required to maintain 90% paralysis ($C_P{}^{ss}{}_{90}$) of 1.13 (0.24) µg ml^{-1}. The clearances of atracurium, estimated by the constant infusion rate required to maintain the steady state plasma concentration, at 50–60 min and during estimation of $C_P{}^{ss}{}_{90}$ were 3.8 (1.0) and 3.9 (1.1) ml kg^{-1} min^{-1} (ns), respectively. The volume of distribution at steady state of atracurium after 1 h of infusion, calculated using the clearance and the area under the plasma concentration–time curve to 1 h, was 130 (50) ml kg^{-1}. These estimates of the pharmacokinetic parameters of atracurium are markedly different from those derived from pharmacokinetic analysis of single bolus dose data. Normalization of the pharmacokinetic parameter estimates by lean body mass decreased interpatient variability and improved precision in comparison with the un-weighted data and normalization by total body weight.

KEY WORDS

Anaesthetic techniques: infusion. Neuromuscular relaxants atracurium. Pharmacokinetics: atracurium

The accurate determination of the pharmacokinetics of a drug may help the anaesthetist to predict the consequences of different dose regimens and design more efficient regimens that are effective with minimal side effects and toxicity [1]. Traditionally, the pharmacokinetic properties of neuromuscular blocking drugs have been investigated after a single bolus dose, with pharmacokinetic models constructed to characterize drug distribution and elimination.

The simplest infusion regimen for an agent to provide relaxation suitable for tracheal intubation and continuous surgical relaxation is:

$$\text{Bolus dose} = C_P{}^{ss}{}_{90} \cdot V^{ss} \qquad (1)$$

$$\text{Infusion rate} = C_P{}^{ss}{}_{90} \cdot Cl \qquad (2)$$

where $C_P{}^{ss}{}_{90}$ = steady state plasma concentration of neuromuscular blocking drug associated with 90% paralysis, V^{ss} = volume of distribution at steady state, and Cl = clearance of the agent [1, 2]. The accuracy of data derived from pharmacokinetic models in order to construct such infusion systems has not been assessed. To the extent that they fail to provide accurate predictions, these models will have to undergo revision [3].

The aim of this study was to measure the pharmacokinetic parameters of atracurium by a model-independent method during continuous infusion, and the $C_P{}^{ss}{}_{90}$ using a previously developed infusion technique which maintained constant muscle paralysis. The estimates of the pharmacokinetic parameters are compared with those published previously from pharmacokinetic analysis of single bolus dose data.

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PATIENTS AND METHODS

Twenty adult patients (11 male) undergoing major surgery gave informed consent to participate in the study, which was approved by the Hospital Board of Medical Research.

Anaesthesia was induced with thiopentone 1–4 mg kg^{-1} and fentanyl 1–5 µg kg^{-1} and maintained with 70 % nitrous oxide in oxygen and continuous infusion of propofol. The infusion of propofol was adjusted and further incremental doses of fentanyl 1–2 µg kg^{-1} were administered as required to maintain adequate anaesthesia. Ventilation was controlled throughout the study to maintain Pa_{CO_2} at 4.7–5.3 kPa. Nasopharyngeal temperature was kept at 35.5–37 °C. The electromyogram (EMG) of the first dorsal interosseous muscle to supramaximal stimulation of the ulnar nerve was measured and recorded by a Datex Relaxograph.

Muscle relaxation was induced initially with suxamethonium 1.0 mg kg^{-1} and maintained by infusion of atracurium. The infusion was via a specially built syringe pump according to a predetermined profile which continually set the infusion rate to maintain stable muscle paralysis and a target plasma concentration when equilibrium between the biophase and plasma had occurred (steady state plasma concentration) [4]. The syringe pump was capable of reading successive memory locations containing the infusion rate data at specific times, and scaling the infusion rate according to patient size and the target plasma concentration. The infusion rate was adjusted for patient lean body mass (LBM), which was estimated using the method of James [5].

For the first 1 h, atracurium was infused to a target C_P^{ss} of 1.0 µg ml^{-1}, with arterial blood samples drawn at 0, 2, 4, 7, 10, 15, 20, 30, 40, 50 and 60 min. Thereafter, the $C_P^{ss}{}_{90}$ of atracurium was estimated by adjusting the target plasma concentration delivered by the infusion to maintain 90 % single twitch inhibition (height of first twitch/height of control twitch, T1/Tc) within a range of 88–92 % [4]. After inhibition of T1/Tc was stable at 88–92 % for 15–20 min, three arterial blood samples were drawn at 5-min intervals, with the first sample taken a minimum of 20 min after alteration of the target plasma concentration. A variation in the plasma atracurium concentration of less than 5 % during the measurement period was necessary to confirm steady state conditions for both estimation of $C_P^{ss}{}_{90}$ and clearance.

Plasma concentrations of atracurium were measured by a high pressure liquid chromatographic (HPLC) technique. The assay was sensitive to 0.03 µg ml^{-1} of plasma atracurium and was linear over the range of the standard curve (0.05–10 µg ml^{-1} in plasma) with a coefficient of variation of 4.1 % at 0.6 µg ml^{-1}.

Data analysis

The clearance of atracurium (*Cl*) was estimated after 50–60 min of infusion and at the time of estimation of the $C_P^{ss}{}_{90}$, during steady state, by the constant infusion rate (*I*a) required to maintain a steady state plasma concentration (C_P^{ss}) such that:

$$Cl = \frac{Ia}{C_P^{ss}} \qquad (3)$$

The volume of distribution of atracurium at steady state (V^{ss}) was estimated using a modification of the method described by Gibaldi and Perrier for a constant rate infusion [6]. V^{ss} was calculated after 1 h of infusion during steady state by:

$$V^{ss} = \frac{X^{ss}}{C_P^{ss}} \qquad (4)$$

where X^{ss} is the amount of drug in the body at steady state. The amount of drug in the body after 1 h is given by the difference between the administered dose (*X*d) and the amount eliminated up to that time [Xe^{0-1}]:

$$X^{ss} = Xd - [Xe^{0-1}] \qquad (5)$$

$$Xe^{0-1} = Cl.\mathrm{AUC}^{0-1} \qquad (6)$$

where AUC$^{0-1}$ is the area under the plasma concentration time curve to 1 h. The area under the curve was estimated using the trapezoidal rule.

The accuracy and precision of the prediction of the plasma concentration at the time of estimation of $C_P^{ss}{}_{90}$, based on the measured plasma concentration after 50–60 min of infusion, was assessed by the bias and mean absolute prediction error. These were calculated from the prediction error using the method described by Maitre and colleagues [7].

The two estimates of clearance in each patient were compared with a paired-sample Student's *t* test. A single-sample Student's *t* test was used to determine if the mean bias estimate for the group differed from zero. $P < 0.05$ was considered significant. Coefficient of variation (SD/mean) was used to describe the degree of interpatient variability in clearance and volume of distribution. Data are presented as mean (SD) unless otherwise stated.

RESULTS

Details of the 20 patients are presented in table I, together with the individual un-weighted estimates of the clearance and volume of distribution at steady state of atracurium estimated after 1 h of infusion.

The mean clearance of atracurium adjusted for patient total body weight (*Cl*.TBW) after 1 h of infusion was 3.8 (1.0) ml kg^{-1} min^{-1} and this decreased precision by 10%, increasing interpatient variability from 23.2% for *Cl* to 25.5% for *Cl*.TBW (coefficient of variation). Mean *Cl*.TBW of atracurium at the time of estimation of $C_P{}^{ss}{}_{90}$ was 3.9 (1.1) ml kg^{-1} min^{-1} and was not significantly different from the estimate at 1 h. The mean clearance of atracurium adjusted for patient LBM (*Cl*.LBM) after 1 h of infusion was 5.4 (0.9) ml kgLBM^{-1} min^{-1} and improved precision by 25.9% *vs* *Cl*, decreasing interpatient variability to 17.2% (coefficient of variation), and improved precision by 32.5% *vs* *Cl*.TBW. The individual values of *Cl*.LBM estimated in the 20 patients after 1 h of infusion are illustrated in figure 1.

Mean V^{ss} of atracurium adjusted for patient TBW (V^{ss}.TBW) after 1 h of infusion was 130 (50) ml kg^{-1} and decreased precision by 0.8%, increasing interpatient variability from 37.5%

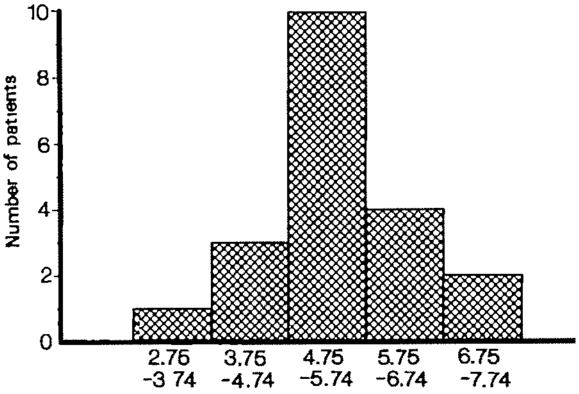

FIG. 1. Estimated plasma clearance of atracurium adjusted for lean body mass (LBM) in 20 patients under propofol anaesthesia.

TABLE I. *Details of the 20 patients studied (mean (SD) age 59.4 (13.2) yr). Total body weight (TBW), lean body mass (LBM) (calculated using the method described by James [5]) and individual un-weighted estimates of clearance (Cl), volume of distribution at steady state (V^{ss}) and the steady state plasma concentration for 90% paralysis by atracurium ($C_P{}^{ss}{}_{90}$)*

Patient No.	TBW (kg)	LBM (kg)	*Cl* (ml min^{-1})	V^{ss} (litre)	$C_P{}^{ss}{}_{90}$ (µg ml^{-1})
1	46	37	230.7	8.9	1.11
2	68	57	255.9	6.81	1.47
3	70	58	267.8	14.09	1.13
4	59	42	234.2	11.07	0.73
5	57	47	318.8	6.64	0.84
6	55	38	227.8	5.68	1.03
7	75	60	324.1	14.46	1.37
8	78	61	406.2	8.32	0.81
9	77	59	283.7	5.73	1.29
10	52	39	197.8	6.34	1.14
11	61	43	212.0	8.28	0.77
12	80	57	212.7	7.39	1.02
13	110	69	340.2	9.64	1.47
14	87	53	356.0	11.36	0.88
15	110	64	327.2	14.75	1.26
16	84	49	186.7	6.72	1.43
17	76	59	399.7	17.72	1.35
18	100	49	238.9	4.47	1.20
19	104	52	274.4	10.82	1.01
20	70	55	306.7	10.21	1.36
Mean (SD)	76 (19)	52 (9)	280 (65)	9.5 (3.6)	1.13 (0.24)

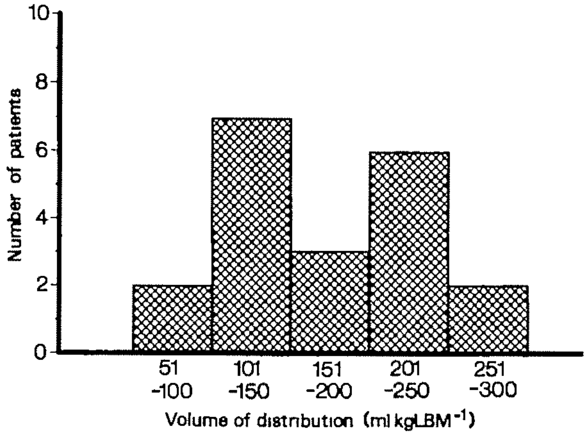

FIG. 2. Estimated volume of distribution at steady state of atracurium adjusted for lean body mass (LBM) in 20 patients under propofol anaesthesia.

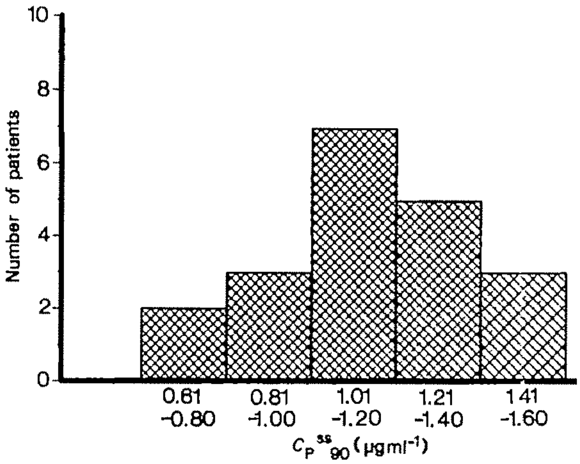

FIG. 3. $C_P{}^{ss}{}_{90}$ of atracurium in 20 patients under propofol anaesthesia following the administration of suxamethonium.

for V^{ss} to 38.2% for V^{ss}.TBW (coefficient of variation). Mean V^{ss} of atracurium adjusted for patient LBM (V^{ss}.LBM) was 181 (60) ml kgLBM^{-1} and improved precision by 13.5% *vs* V^{ss}, decreasing interpatient variability to 32.8% for V^{ss}.LBM (coefficient of variation), and improved precision by 14.1% *vs* V^{ss}.TBW. Figure 2 illustrates the values of V^{ss}.LBM of atracurium calculated after 1 h of infusion for individual patients.

Table II compares the mean estimates for *Cl*.TBW and V^{ss}.TBW after 1 h of infusion with previously published estimates based on pharmacokinetic analysis of single bolus doses.

Mean $C_P{}^{ss}{}_{90}$ of atracurium in the 20 patients under propofol–nitrous oxide anaesthesia following administration of suxamethonium was 1.13 (0.24) μg ml^{-1} with a 95% confidence interval of individual results of 0.63–1.63 μg ml^{-1}. The interpatient variability for $C_P{}^{ss}{}_{90}$ was 21.3% (coefficient of variation). Figure 3 illustrates the individual patient values.

The actual infusion rate of atracurium required to maintain 90% paralysis during estimation of the $C_P{}^{ss}{}_{90}$ was 4.25 (1.11) μg kg^{-1} min^{-1}. The theoretical maintenance infusion rate for 90% paralysis, based on the $C_P{}^{ss}{}_{90}$ and *Cl* estimated at 50–60 min in this study, was 4.29 μg kg^{-1} min^{-1}.

The ability to predict the plasma concentration at the time of estimation of $C_P{}^{ss}{}_{90}$ based on measured plasma concentration after 50–60 min infusion was good, with an overall mean bias of −1.6 (9.9)% (ns) and an overall mean absolute prediction error of 12.5 (11.8)%. This observation is consistent with the pharmacokinetics of atracurium being linear within the limits of the concentrations measured (0.73–1.47 μg ml^{-1}).

DISCUSSION

The apparent volume of distribution and clearance of a drug are useful pharmacokinetic parameters that are, respectively, the proportionality constant relating drug concentration in plasma to

TABLE II. *Pharmacokinetic parameters of atracurium (mean (SD)). Cl.TBW = clearance adjusted for total body weight; V^{ss}.TBW = volume of distribution at steady state adjusted for total body weight; Vd.TBW = apparent volume of distribution adjusted for total body weight*

Source	*n*	*Cl*.TBW (ml kg^{-1} min^{-1})	V^{ss}.TBW (ml kg^{-1})	*V*d.TBW (ml kg^{-1})
Present study	20	3.8 (1.0)	130 (50)	—
Cook and colleagues [8]	6	4.7 (0.1)	—	166 (5)
Ward and Weatherley [9]	6	5.5 (0.7)	—	153 (32)
Fahey and colleagues [10]	10	6.1 (0.9)	—	182 (38)
Ward and colleagues [11]	12	5.5 (1.1)	—	157 (24)

the amount of drug in the body and a measure of the efficiency of drug elimination. Estimation of clearance by a constant rate infusion maintaining a steady state plasma concentration is a well recognized and accurate method for its determination [12]. The only assumption with this method is that the measurement is made under steady state condition when, after complete distribution of the drug, a constant rate of drug delivery maintains a constant plasma concentration by an equivalent rate of drug loss. Steady state conditions in this study were confirmed by a stable arterial plasma concentration, with less than a 5% drift, during a constant rate of drug delivery. It is unlikely that the 30% lower estimate of clearance found in this study compared with previous published estimates derived from pharmacokinetic analysis of single bolus doses (table II) was caused by inaccuracies with this method [8–11]. If the measurements had not been made under steady state conditions, the continuing redistribution of the drug would have caused the clearance to be overestimated.

It is not essential that the rate of drug delivery preceding the development of steady state conditions is constant, as steady state can occur with an initial variable rate infusion becoming constant when distribution of a drug is complete [12]. The infusion profile for atracurium used in this study resulted in steady state conditions after 39 min of infusion, compared with 80–100 min with a constant rate infusion. Theoretically, for atracurium with a distribution half-life of 3.4 min [10], steady state conditions could occur after 14–17 min.

The apparent volume of distribution at steady state of atracurium was calculated in this study by estimating the amount of drug in the body at the time of a given steady state plasma concentration. The clearance and the area under the plasma concentration–time curve to that time were used to calculate the amount of drug eliminated and hence the amount remaining from the known total dose administered [6]. The method assumes that the clearance of atracurium is linear within the limits of the plasma concentration of atracurium achieved, and is not subject to time-dependent changes. This hypothesis is supported by the finding that the estimates of the clearance of atracurium were similar at 50–60 min and when the $C_{\mathrm{P}}{}^{\mathrm{ss}}{}_{90}$ was estimated (90–120 min) with different plasma concentrations.

The derivation of a pharmacokinetic model for a drug from a single bolus dose requires several assumptions, including elimination occurring only from one compartment and linearity of drug elimination between a plasma concentration approaching zero and the maximum plasma concentration following the bolus dose. Atracurium undergoes hydrolysis in both the peripheral and the central compartments [13]. As a result, it is impossible to derive a pharmacokinetic model or calculate the volume of distribution at steady state of atracurium from single bolus dose data, as there is no unique solution to its pharmacokinetic model [11, 14]. The "apparent" volume of distribution (*V*d) of atracurium derived from single bolus doses was derived by assuming incorrectly that atracurium is eliminated only from the central compartment [8–11, 14]. *V*d tends to overestimate the volume of distribution at steady state, particularly when the drug has a short elimination half-life, as does atracurium [15]. The clearance of atracurium can be calculated by non-compartmental methods from single bolus dose data. However, modelling atracurium as a single drug when it is a mixture of 10 isomers with varying clearance rates may induce significant methodological errors [16]. Overall, the pharmacokinetic parameters derived from a single bolus dose are subject to several potential sources of error and may not apply at therapeutic concentrations or during continuous infusion [17, 18]. The clearance and volume of distribution of atracurium were determined in this study under actual surgical conditions and at therapeutic concentrations. The theoretical maintenance infusion rate required to maintain 90% paralysis was 4.29 ml kg^{-1} min^{-1} using our estimates of clearance and $C_{\mathrm{P}}{}^{\mathrm{ss}}{}_{90}$ and 5.3–6.9 ml kg^{-1} min^{-1} using clearance estimated from single bolus dose data [8–11] and our estimate of $C_{\mathrm{P}}{}^{\mathrm{ss}}{}_{90}$, compared with the actual rate found in this study of 4.25 ml kg^{-1} min^{-1}.

Adjusting drug dose on the basis of individual patient size is an important method for improving precision of dosing. Traditionally, for neuromuscular blocking drugs this has been achieved by relating dose to the total body weight of the patient, despite good evidence that this relationship is poor [19, 20]. The lack of improvement in the precision of the estimates of clearance and volume of distribution of atracurium with normalization by total body weight *vs* the un-weighted data found in this study, suggests that the administration of a fixed dose to adult patients may have a dosing precision similar to that based on total body weight. Dosage of atracurium in this study was adjusted by patient lean body mass, as we have shown previously that this improved the precision of dosing in a heterogenous population compared with dosage based on total body weight [21]. Further support for its use is the finding that normalization of the pharmacokinetic parameters for atracurium by lean body mass in comparison with the un-weighted data and normalization by total body weight decreased interpatient variability and improved precision.

The prior administration of suxamethonium has been shown to potentiate competitive neuromuscular blockers, with the effect persisting for at least 30 min after administration of suxamethonium [22, 23]. In this study, the $C_{\mathrm{P}}^{ss}{}_{90}$ of atracurium estimated under propofol–nitrous oxide anaesthesia, 90–120 min after administration of suxamethonium, was similar to our previous estimate in the absence of suxamethonium (1.13 *vs* 1.04 μg ml^{-1}; ns) [4]. This finding is consistent with the observation of d'Hollander and colleagues that the effect of suxamethonium on the dose–effect relationship of vecuronium has disappeared totally in vecuronium infusions lasting more than 90 min [24].

In summary, this study has determined the clearance and volume of distribution of atracurium at steady state during continuous infusion by a model-independent method. These estimates are markedly different from those derived from pharmacokinetic analysis of single bolus dose data. This suggests that extrapolation of single dose pharmacokinetic data to the design of infusion regimens for atracurium and perhaps other neuromuscular blocking drugs may be prone to large errors.

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PHARMACODYNAMICS OF ATRACURIUM DURING PROPOFOL, THIOPENTONE AND OPIOID ANAESTHESIA

G. H. BEEMER, A. R. BJORKSTEN AND D. P. CRANKSHAW

SUMMARY

We have assessed in 20 patients the accuracy and precision of an infusion profile for atracurium, which continually set the infusion rate to maintain stable muscle paralysis and a target steady state plasma concentration, when equilibrium between the biophase and plasma had occurred. Muscle paralysis was stable after 20 min, with a mean absolute drift in muscle paralysis in the succeeding 40 min of 0.13 (SD 0.07)% T1/Tc (height of first twitch/height of control twitch) per min. The plasma samples after 30 min, which were assessed empirically as being in equilibrium with the biophase, had an overall mean bias of 8.0 (SEM 3.7)% ($P < 0.05$) and an overall mean absolute prediction error of 16.4 (SEM 2.5)% from the target steady state concentration being delivered by the infusion. The profile was then used to estimate the steady state plasma concentration of atracurium required to maintain 90% paralysis ($C_P^{ss}{}_{90}$), by manually adjusting the delivered target concentration of the infusion until muscle paralysis was stable at 88–92% inhibition of T1/Tc for 15–20 min, with three plasma samples taken over the next 10 min. Measurements were completed within 60–90 min. The mean $C_P^{ss}{}_{90}$ of atracurium with propofol was 1.039 (SD 0.224) μg ml^{-1} ($n = 10$), with thiopentone 1.334 (0.378) μg ml^{-1} ($n = 10$), and with opioid anaesthesia 0.915 (0.221) μg ml^{-1} ($n = 10$). These differences in the $C_P^{ss}{}_{90}$ explain some of the variability in response which occurs with neuromuscular blocking drugs. The technique enables the $C_P^{ss}{}_{90}$ of a myoneural blocker to be determined by a simple model-independent method.

KEY WORDS

Anaesthetics, intravenous: propofol, thiopentone. Anaesthetic techniques. infusion Neuromuscular relaxants: atracurium. Pharmacodynamics · atracurium.

The magnitude and duration of muscle paralysis following administration of a given dose of a competitive neuromuscular blocking drug in an individual patient is unpredictable. Katz found that tubocurarine 0.1 mg kg^{-1} caused no block in 6%, and 100% block in 7% of patients [1]. This variability in response is probably the chief contributing factor in anaesthetic morbidity and mortality associated with neuromuscular blocking drugs. Pharmacokinetic and pharmacodynamic studies allow the identification of the sources of this variability, enabling the anaesthetist better to anticipate patient responses, and thus reduce the likelihood of excessive paralysis and residual curarization [2].

Accurate estimation of the pharmacodynamics of myoneural blockers, in particular, is difficult with current research techniques. Combined pharmacokinetic–dynamic models have been developed to make allowance for the temporal disequilibrium between the plasma and the biophase (neuromuscular effector site), to enable pharmacodynamics to be studied under non-steady state conditions [3–8]. The technical difficulties associated with these methods have resulted in a limited number of patients having been studied, with only two pharmacokinetic–dynamic models for normal patients, based on a study of eight patients and four patients, developed for atracurium [7, 8].

The aim of this study was to develop a simple alternative technique to characterize the pharmacodynamics of a neuromuscular blocker by estimating the effective steady state plasma concentration for 90% paralysis ($C_P{}^{ss}{}_{90}$) using an

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infusion regimen to maintain constant muscle paralysis. The method was utilized to determine the $C_P{}^{ss}{}_{90}$ of atracurium during propofol, thiopentone and opioid anaesthesia.

PATIENTS AND METHODS

Fifty adult patients undergoing major surgery gave informed consent to participate in the study, which was approved by the Hospital Board of Medical Research. Routine preoperative biochemical tests were used to exclude patients with evidence of hepatic or renal dysfunction.

The electromyogram (EMG) of the first dorsal interosseous muscle to supramaximal stimulation of the ulnar nerve was measured and recorded with a Datex Relaxograph. The test hand was immobilized with no resting tension and wrapped in a towel with Medi-trace pellet electrodes placed 10–15 min before induction of anaesthesia. After anaesthesia was induced and before atracurium was administered, control twitch height (Tc) and a train-of-four fade ratio (T4:T1) were established. Subsequently, a train-of-four stimulation was delivered every 12 s with the single twitch inhibition (T1/Tc) and T4:T1 recorded. Baseline was stabilized for 3–5 min, with T1/Tc and T4:T1 at 100% before the onset of muscle paralysis.

A specially built syringe pump capable of reading successive memory locations, containing the infusion rate data, at specific times and adjusting the infusion rate according to patient size and the target plasma concentration, was used to infuse atracurium [9]. Atracurium was infused according to a profile defined in table I, which continually set the infusion rate to maintain a constant biophase concentration, as assessed by stable muscle paralysis. When equilibrium had occurred between the biophase and plasma, a target steady state plasma concentration was maintained thereafter by the infusion. The technique used to develop the profile is briefly outlined in the Appendix, and is based on a modification of the plasma drug efflux method [9]. The infusion rate was adjusted for by patient lean body mass (LBM), estimation of which, for each patient, was based on the method of James [10].

The precise infusion rate delivered to an individual patient for a specific time interval (Q_1) is the rate defined in the profile for that interval (Qp_1) adjusted for patient LBM and the target

TABLE I. *The infusion profile used in this study. The profile was adjusted to achieve a target plasma concentration of atracurium, after equilibrium between the biophase and plasma had occurred, of 1.0 μg ml⁻¹ in a "patient" of 1 kg lean body mass (LBM)*

Time (min)	Infusion profile (μg min^{-1} kgLBM^{-1})	Time (min)	Infusion profile (μg min^{-1} kgLBM^{-1})
0–1	200	21–22	7.40
1–2	8.68	22–23	7.30
2–3	8.68	23–24	7.20
3–4	8.68	24–25	7.10
4–5	8.68	25–26	7.00
5–6	8.68	26–27	6.88
6–7	8.68	27–28	6.78
7–8	8.41	28–29	6.68
8–9	8.15	29–30	6.58
9–10	7.88	30–31	6.47
10–11	7.83	31–32	6.35
11–12	7.78	32–33	6.23
12–13	7.72	33–34	6.12
13–14	7.67	34–35	6.02
14–15	7.62	35–36	5.90
15–16	7.62	36–37	5.78
16–17	7.62	37–38	5.67
17–18	7.62	38–39	5.55
18–19	7.62	39–40	5.43
19–20	7.62	40–∞	5.43
20–21	7.52		

steady state concentration of atracurium ($C_P t$) and is given by:

$$Q_1 = Qp_1 . C_P t . \mathrm{LBM}. \tag{1}$$

In the first part of the study, the accuracy of the profile in maintaining both stable muscle paralysis and the target plasma concentration was assessed in 20 patients. Anaesthesia was induced with thiopentone 1–4 mg kg^{-1} and fentanyl 5–20 µg kg^{-1} and maintained with 70% nitrous oxide and incremental doses of fentanyl. Atracurium was infused for 1 h according to a profile to maintain stable muscle paralysis and a target steady state plasma concentration of 1.0 µg ml^{-1} when equilibrium between the biophase and plasma had occurred. Arterial blood samples were obtained at 0, 2, 4, 7, 10, 15, 20, 30, 40, 50 and 60 min. The patients received other adjuvants, including diazepam and droperidol, but excluding volatile anaesthetic agents, on the basis of clinical signs and in accordance with current practice. Ventilation was controlled throughout the study to maintain Pa_{CO_2} in the range 4.7–5.3 kPa. Nasopharyngeal temperature was kept at 35.5–37 °C.

In the second part of the study, the $C_P{}^{ss}{}_{90}$ of atracurium was assessed during propofol, thiopentone and fentanyl anaesthesia with 10 patients in each group. Atracurium was infused initially according to the profile to achieve a target steady state plasma concentration of 1.0–1.5 µg ml^{-1} when equilibrium between the biophase and plasma had occurred. Following the onset of stable muscle paralysis, within 15–20 min of commencing the infusion, the target steady state plasma concentration delivered by the infusion was adjusted to maintain 90% inhibition of T1/Tc, within a range of 88–92%. If the paralysis was less than 90%, the patient was administered a small bolus of atracurium (1–3 mg) and the target concentration increased. If the paralysis was greater than 90%, the infusion was stopped and was recommenced at a lesser concentration when T1/Tc inhibition was 95%. This process was repeated until inhibition of T1/Tc was stable at 88–92% for 15–20 min. Three arterial blood samples were obtained at 5-min intervals, with the first sample being a minimum of 20 min after the final alteration of the infusion rate. Variation in the plasma concentration of atracurium of less than 5% confirmed steady state conditions for estimation of $C_P{}^{ss}{}_{90}$.

Anaesthesia was maintained with 70% nitrous oxide in oxygen and continuous infusion of propofol (maintenance infusion rate 0.05–0.15 mg kg^{-1} min^{-1}), continuous infusion of thiopentone (to maintain an arterial plasma concentration of thiopentone 10 µg ml^{-1} [9], maintenance infusion rate 55–95 µg kg^{-1} min^{-1}), or incremental doses of fentanyl 5–10 µg kg^{-1} (total dose 30–50 µg kg^{-1} within the first 60 min).

TABLE II. *Patient characteristics (mean (SD)). LBM = lean body mass*

Study	*n*	Age (yr)	Sex (M/F)	Weight (kg)	LBM (kg)
Part 1	20	56 (13)	11/9	69 (13)	50 (8)
Part 2					
Propofol	10	62 (11)	7/3	68 (20)	51 (11)
Thiopentone	10	49 (12)	6/4	76 (22)	52 (11)
Opioid	10	54 (10)	6/4	76 (8)	58 (5)

Plasma concentrations of atracurium were measured by a high pressure liquid chromatography (HPLC) technique. The assay was sensitive to 0.03 µg ml^{-1} of plasma atracurium and was linear over the range of the standard curve (0.05–10 µg ml^{-1} in plasma) with a coefficient of variation of 4.1% at 0.06 µg ml^{-1}.

Data analysis

The accuracy and precision of the profile in achieving the target steady state plasma concentration of atracurium was assessed by the bias and mean absolute prediction error. These were calculated from the prediction error (PE, as a percentage) using the method described by Maitre and colleagues [11]. The prediction error was modified as follows:

$$\mathrm{PE} = \frac{C_P\mathrm{m} - C_P\mathrm{t}}{C_P\mathrm{t}} \times 100 \tag{2}$$

where $C_P\mathrm{m}$ was the measured arterial concentration.

Student's *t* test was used to assess if the mean bias estimates for the group differed from zero. Student's *t* test with Bonferroni correction for multiple comparisons was used to assess the significance of the effect of anaesthetic agents on the $C_P{}^{ss}{}_{90}$ of atracurium. $P < 0.05$ was considered significant. Data are presented as mean (SD) unless stated otherwise.

RESULTS

Patient data are presented in table II. Figure 1 shows the results of the infusion of atracurium according to the infusion profile in a representative patient from the first part of the study. The mean plasma concentration of atracurium with 95% confidence limits in the 20 patients is illustrated in figure 2. Figure 3 shows the resultant muscle paralysis with 95% confidence intervals. The mean muscle paralysis in the 20 patients at 60 min was 11.5% T1/Tc, 95% of patients falling within the range 3–20%. The infusion profile maintained a relatively constant biophase concentration following onset of maximum muscle paralysis 15–20 min after commencing the infusion, as shown by a mean absolute drift in muscle paralysis in the succeeding 40 min of 0.13 (0.07)% T1/Tc min^{-1}, with most of this drift occurring between 20 and 30 min (fig. 3). The plasma concentration became constant 30 min after starting the infusion, with a mean absolute drift of 0.51 (0.40)% min^{-1} between 30 and 60 min. Thus plasma samples taken 30 min after starting the infusion were assessed empirically as

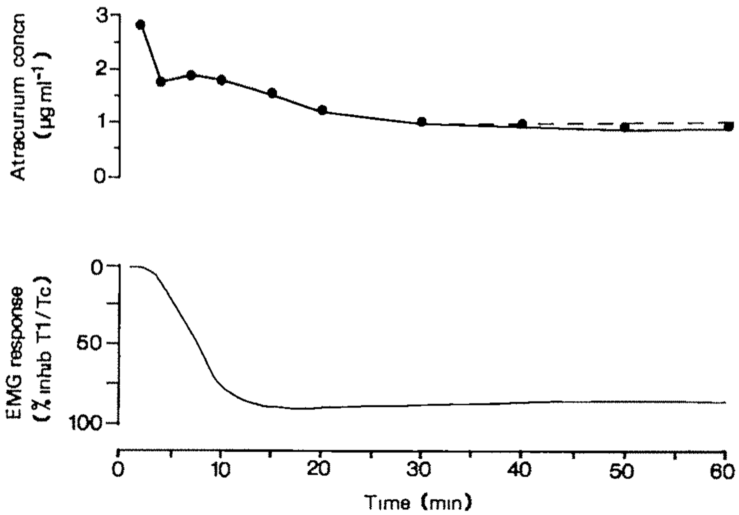

FIG. 1. Upper graph: measured plasma concentrations of atracurium in a 67-yr-old patient (total body weight 63 kg, LBM 44 kg) in whom atracurium was infused according to the profile in the first part of the study, along with the target plasma concentration of atracurium which was to be maintained after 30 min (dashed line). Lower graph: resulting muscle paralysis (% inhibition of T1/Tc assessed by EMG).

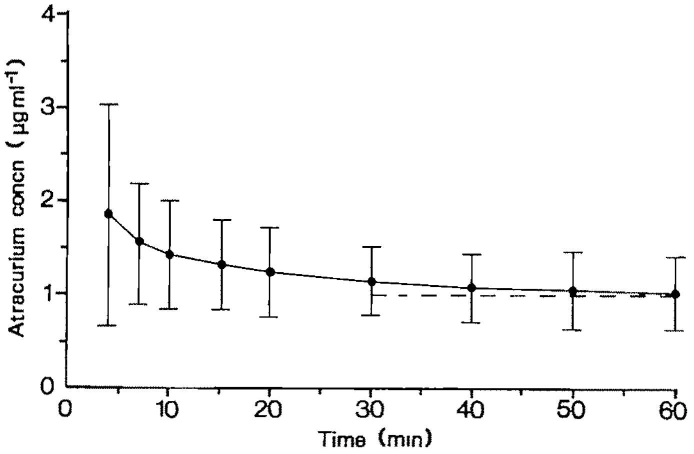

FIG. 2. Mean plasma concentration of atracurium (●) and 95% confidence intervals (vertical bars) for the 20 patients in whom atracurium was infused in the first part of the study. The dashed line represents the target plasma concentration of 1.0 $\mu g\ ml^{-1}$ which was to be maintained after 30 min, after equilibrium between the plasma and biophase had occurred.

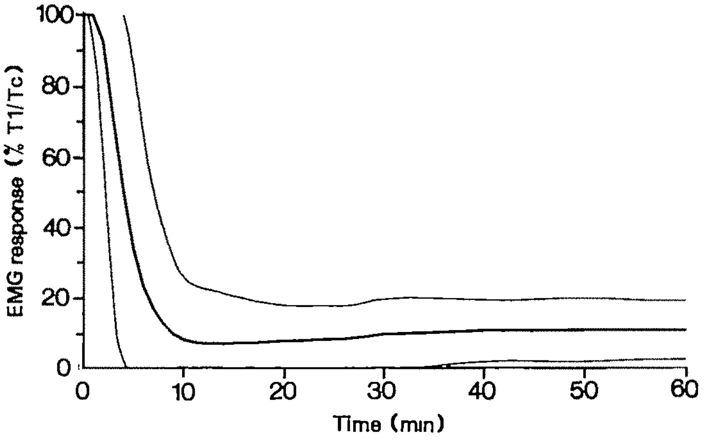

FIG. 3. Mean muscle paralysis as % inhibition of T1/Tc assessed by EMG (thick line) with 95% confidence interval (fine lines) in the 20 patients in whom atracurium was infused in the first part of the study.

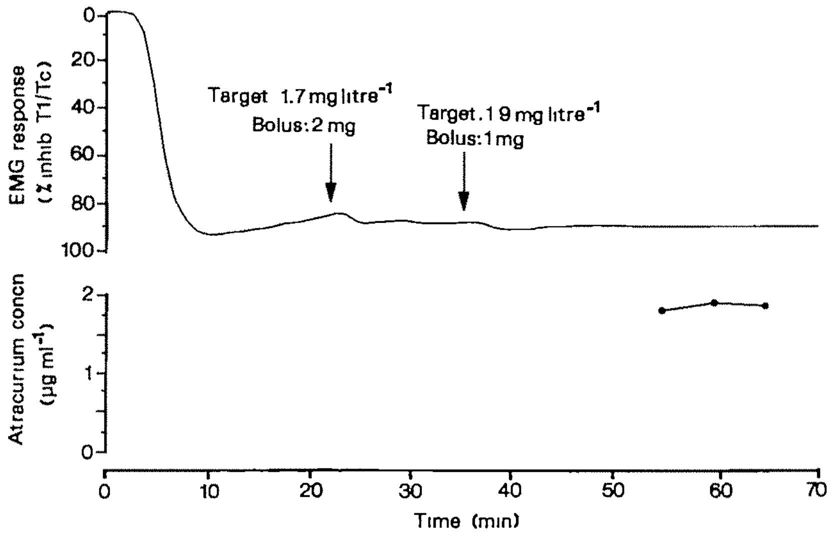

FIG. 4. Upper graph: muscle paralysis as % inhibition of T1/Tc assessed by EMG during estimation of $C_{\mathrm{P}\,90}^{\mathrm{ss}}$ of atracurium during propofol anaesthesia in a representative male patient. The initial target steady state plasma concentration of atracurium was 1.3 µg ml^{-1}, which was changed to 1.5 µg ml^{-1} at 22 min and to 1.9 µg ml^{-1} at 35 min. Lower graph: plasma concentration of atracurium at 55, 60 and 65 min, when muscle paralysis was stable at 11% inhibition T1/Tc. $C_{\mathrm{P}\,90}^{\mathrm{ss}}$ of atracurium during propofol anaesthesia was estimated to be 1.851 µg ml^{-1} in this patient.

in equilibrium with the biophase. The overall mean bias for these plasma samples was 8.0 (SEM 3.7)% ($P < 0.05$) and the overall mean absolute prediction error was 16.4 (SEM 2.5)% in achieving the target steady state plasma concentration.

The method of estimation of $C_{\mathrm{P}\,90}^{\mathrm{ss}}$ of atracurium, as used in the second part of the study, is illustrated in figure 4 for a representative patient. The infusion rate was adjusted twice until inhibition of T1/Tc was stable at 88–92% for 20 min, with blood samples taken to measure the steady state plasma concentration of atracurium. The concentration was relatively constant during this sampling period in all patients, with less than the maximum allowable variation of 5%. The overall mean bias of these plasma samples from the target steady state plasma concentration being delivered by the infusion profile was −2.5

TABLE III. *Individual estimates of the $C_P^{ss}{}_{90}$ of atracurium during propofol anaesthesia, together with the individual arterial plasma concentrations of atracurium and the mean measured twitch depression during the sampling period*

Patient No.	Plasma arterial concn ($\mu g\ ml^{-1}$)			Twitch depression (% of control)	$C_P^{ss}{}_{90}$ ($\mu g\ ml^{-1}$)
	Sample 1	Sample 2	Sample 3		
1	0.844	0.844	0.831	90	0.840
2	0.894	0.872	0.876	89	0.881
3	1.020	0.988	0.996	89	1.001
4	0.732	0.711	0.752	88	0.732
5	0.877	0.840	0.861	92	0.859
6	1.452	1.460	1.488	91	1.467
7	1.110	1.158	1.160	90	1.143
8	1.020	1.053	1.026	90	1.033
9	1.174	1.187	1.214	89	1.192
10	1.263	1.228	1.246	89	1.246
Mean (SD)					1.039 (0.224)

TABLE IV. *Individual estimates of the $C_P^{ss}{}_{90}$ of atracurium during thiopentone anaesthesia, together with the individual arterial plasma concentrations of atracurium and the mean measured twitch depression during the sampling period*

Patient No.	Plasma arterial concn ($\mu g\ ml^{-1}$)			Twitch depression (% of control)	$C_P^{ss}{}_{90}$ ($\mu g\ ml^{-1}$)
	Sample 1	Sample 2	Sample 3		
1	1.191	1.208	1.174	89	1.191
2	1.846	1.857	1.850	89	1.851
3	1.333	1.354	1.381	91	1.356
4	0.917	0.953	0.949	91	0.940
5	2.000	2.071	1.995	90	2.022
6	0.921	0.919	0.923	91	0.921
7	1.065	1.029	1.048	91	1.047
8	1.499	1.541	1.481	89	1.507
9	1.460	1.430	1.446	92	1.445
10	1.079	1.075	1.027	90	1.060
Mean (SD)					1.334 (0.378)

(SEM 5.6)% (ns), and the overall mean absolute prediction error was 24.1 (SEM 3.4)%. Measurements were completed within 60–90 min.

The individual estimates of the $C_P^{ss}{}_{90}$ of atracurium in 10 patients during propofol, thiopentone and opioid anaesthesia are listed in tables III–V. The $C_P^{ss}{}_{90}$ of atracurium during propofol anaesthesia was 1.039 (0.224) $\mu g\ ml^{-1}$, during thiopentone anaesthesia 1.334 (0.378) $\mu g\ ml^{-1}$, and during fentanyl anaesthesia 0.915 (0.221) $\mu g\ ml^{-1}$ (fentanyl *vs* thiopentone, $P < 0.05$; others ns). The maintenance infusion rate of atracurium required to maintain 90% inhibition of T1/Tc with propofol was 4.44 (0.78) $\mu g\ kg^{-1}\ min^{-1}$, with thiopentone 5.62 (1.23) $\mu g\ kg^{-1}\ min^{-1}$, and with opioid anaesthesia 3.86 (0.51) $\mu g\ kg^{-1}\ min^{-1}$.

DISCUSSION

Pharmacodynamic investigation of neuromuscular blocking drugs attempts to define the relationship between the concentration of the agent in the biophase and the degree of muscle paralysis. Unfortunately, the concentration of the drug in the biophase cannot be measured directly. The use of plasma concentration induces a distributional hysteresis because of delay in equilibrium between the biophase and plasma; this obscures the pharmacodynamic relationship [3]. The hysteresis can be corrected either by the development of a pharmacokinetic–dynamic model or by performing multiple steady state experiments. The complex technical requirements

TABLE V. *Individual estimates of the* $C_P{}^{ss}{}_{90}$ *of atracurium during fentanyl anaesthesia, together with the individual arterial plasma concentrations of atracurium and the mean measured twitch depression during the sampling period*

Patient No.	Plasma arterial concn (μg ml^{-1}) Sample 1	Sample 2	Sample 3	Twitch depression (% of control)	$C_P{}^{ss}{}_{90}$ (μg ml^{-1})
1	0.900	0.930	0.942	90	0.924
2	0.903	0.864	0.928	90	0.898
3	0.700	0.750	0.730	90	0.727
4	1.215	1.190	1.202	89	1.202
5	1.283	1.290	1.255	90	1.276
6	0.981	0.970	1.002	88	0.984
7	0.734	0.709	0.726	90	0.723
8	1.019	1.050	1.004	90	1.024
9	0.835	0.838	0.844	88	0.839
10	0.555	0.542	0.555	91	0.551
Mean (SD)					0.915 (0.221)

of pharmacokinetic–dynamic models and their many inherent limitations [12] have restricted their usefulness.

For steady state conditions to apply, measurements must be performed when the biophase and plasma are in equilibrium. At steady state the plasma concentration, although not equal to the biophase concentration, uniquely reflects it and may be used to estimate the pharmacodynamics of myoneural blockers [5]. In this study we have characterized the pharmacodynamics of atracurium at only one level of paralysis, by estimation of the $C_P{}^{ss}{}_{90}$. This represents the steady state plasma concentration of the blocker which is desirable for surgical relaxation in normal patients [13]; 90% paralysis of adductor pollicis is considered optimal for intra-abdominal surgery [14].

A critical requirement for this method was that equilibrium between the plasma and biophase must have occurred at the time of estimation of $C_P{}^{ss}{}_{90}$. A first order rate constant (k_{eo}) characterizes the rate at which the biophase equilibrates with the plasma. The half-time for equilibration between the plasma and biophase ($T_{\frac{1}{2}}^{k_{eo}}$) has been estimated to be 4.7 min for tubocurarine [3], 3.3 min for pancuronium [4] and 4.8 min for fazadinium during nitrous oxide–opioid anaesthesia [4]. We have observed similar values for atracurium [unpublished observation]. Theoretically, the time required for equilibration between the plasma and biophase following a change in the plasma concentration of a neuromuscular blocker is approximately four times the $T_{\frac{1}{2}}^{k_{eo}}$, and hence is approximately 20 min for blocking drugs under nitrous oxide–opioid anaesthesia. We confirmed this estimation empirically in the first part of this study, where, in the presence of stable muscle paralysis for 20 min, and hence a constant biophase concentration, the arterial concentration became constant. Therefore, in the second part of the study, to ensure equilibrium between the biophase and plasma, $C_P{}^{ss}{}_{90}$ was estimated only after the biophase concentration had remained constant for 20 min as indicated by stable muscle paralysis. In addition, a constant arterial concentration was assessed by serial estimation of plasma concentration of atracurium over the measurement interval. All patients were within the maximum allowable drift of 5% in the plasma concentration of atracurium over the 10-min measurement interval which we considered compatible with equilibrium conditions. This criterion is quite strict, given that the HPLC assay has a coefficient of variation of approximately 4%.

The infusion profile developed for this study is a useful research tool as it facilitates study under steady state conditions. Equilibrium between the biophase and plasma occurred 30 min after commencing the infusion, compared with 80–100 min for a constant rate infusion of atracurium. This enabled estimation of the $C_P{}^{ss}{}_{90}$ within 60–90 min under relatively stable conditions before other factors which may modify the pharmacodynamics of neuromuscular blocking drugs occurred, such as hypothermia or fluid and electrolyte changes. The maintenance of a constant biophase concentration by the infusion profile resulted in adequate muscle paralysis after 5–10 min, compared with 15–25 min for an infusion profile which maintained a constant plasma concentration. The overall simplicity of the method allows the $C_P^{ss}{}_{90}$ of a neuromuscular blocking drug to be estimated in large patient numbers.

The accuracy of the infusion profile in maintaining a target steady state plasma concentration, after equilibrium between the biophase and plasma had occurred, appears to be comparable to advanced drug delivery systems which utilize a computer-controlled infusion pump [15–17]. This suggests that an infusion profile for a myoneural blocker may be useful also in routine clinical practice, by allowing more precise control of drug delivery. While the profile developed for this study is not suitable, because of slow onset of muscle paralysis as the initial dose was limited to avoid marked overshoot in the desired degree of paralysis, a profile for clinical use could be developed readily using the method outlined in the Appendix. The positive bias of 8% with this profile suggests that its accuracy could be improved by further iteration.

Neuromuscular block in this study was measured by the EMG of the first dorsal interosseous muscle following supramaximal stimulation of the ulnar nerve at the wrist. This has been shown to be equivalent to the isometric recording of the mechanical response of adductor pollicis under nitrous oxide–opioid anaesthesia [18, 19]. Baseline drift of the EMG was minimized by not administering volatile anaesthetic agents, careful preparation and placement of recording electrodes 10 min before establishing the control reading (Tc), and by keeping the hand warm and immobile. Stability was confirmed further by allowing baseline to be stabilized for 3–5 min before onset of muscle paralysis [20].

The $C_P^{ss}{}_{90}$ of atracurium estimated in this study appears to be comparable to that derived from complex pharmacokinetic–dynamic models. The estimated $C_P^{ss}{}_{90}$ of atracurium during halothane anaesthesia was 1.09 $\mu g\ ml^{-1}$ from a pharmacokinetic–dynamic model developed in eight patients [7], and 1.08 $\mu g\ ml^{-1}$ during nitrous oxide–fentanyl anaesthesia from a study of four patients [8]. Our estimate of the $C_P^{ss}{}_{90}$ under nitrous oxide–opioid anaesthesia is 0.92 $\mu g\ ml^{-1}$. This is consistent with clinical observations that the pharmacodynamics of atracurium are similar during opioid and halothane anaesthesia [21, 22]. The statistically significant difference in the estimated $C_P^{ss}{}_{90}$ found in this study during thiopentone and fentanyl anaesthesia has not been reported previously, but does explain some of the variability in response which occurs with neuromuscular blockers. In particular, this may explain the previous observation that the pharmacodynamics of such drugs are less variable during volatile anaesthesia than i.v. anaesthesia [3]. In that study, patients during i.v. anaesthesia received highly variable incremental doses of thiopentone [3]. In contrast with fentanyl and perhaps other i.v. agents, thiopentone appears to have a relatively antagonistic effect on the pharmacodynamics of neuromuscular blocking drugs, as suggested by the greater $C_P^{ss}{}_{90}$ of atracurium.

In conclusion, this study has utilized an infusion profile to estimate the $C_P^{ss}{}_{90}$ of atracurium under various anaesthetic conditions. The technique enables the $C_P^{ss}{}_{90}$ to be determined by a model-independent method and its simplicity allows large numbers of patients to be studied, in contrast to existing research techniques. Such data should permit the design of more accurate infusion regimens for neuromuscular blocking drugs.

APPENDIX

In this Appendix, we present the method used to develop the infusion profile used in this study. The profile was designed to maintain a constant biophase concentration of atracurium, as indicated by stable muscle paralysis, and a target steady state plasma concentration after equilibrium between the biophase and plasma had occurred. An iterative approach was used, whereby an initial arbitrary infusion profile was modified in successive groups of patients to produce an infusion profile with the desired characteristics. The initial arbitrary profile was infused to a small group of patients, with serial estimations of the plasma concentration of atracurium and continuous measurement of the degree of muscle paralysis. The profile was modified using two criteria.

First, the shape of the profile was adjusted to maintain stable muscle paralysis. The loading dose was decreased to avoid 100% muscle paralysis, with the profile in turn adjusted to maintain the degree of paralysis achieved by the loading dose in that patient. The infusion rate was altered by assuming a linear relationship between the infusion rate and paralysis, and empirically allowing for the delay in equilibrium between the plasma and biophase by altering the infusion rate 5–10 min before the change in muscle paralysis occurred in the previous iteration. A new infusion profile was thus generated for each patient ($Ia(t)$). A line of best fit was produced for the group to generate an interim profile ($Iag(t)$), empirically shaped to maintain stable paralysis.

Second, the infusion profile was modified to achieve the target plasma concentration, when equilibrium had occurred between the biophase and plasma, using a modification of the plasma drug efflux method [9]. Equilibrium between the plasma and biophase was considered to have occurred when, in the presence of constant muscle paralysis, the plasma concentration of atracurium became constant. If equilibration could not be assessed empirically, equilibrium was considered to occur 30 min after starting the infusion [3, 4]. A dimensionless scaling factor (F) was derived to modify the infusion profile developed using the first criterion. For each sampling point at equilibrium between the biophase and plasma, F_i was calculated as follows:

$$F_i = \frac{I_i\ C_{\mathrm{P}}\mathrm{t}}{I\mathrm{a}_i . C_{\mathrm{P}}\mathrm{m}_i}, \qquad (1)$$

where $C_{\mathrm{P}}\mathrm{t}$ = target steady state plasma concentration; $C_{\mathrm{P}}\mathrm{m}_i$ = the measured arterial concentration at the ith sampling point; I_i = corresponding infusion rate at that time; $I\mathrm{a}_i$ = infusion rate at the corresponding time in the new profile developed using the first criterion in this patient. Individual values of F_i were averaged to produce a mean scaling factor for the patient and for the group ($F\mathrm{g}$). $F\mathrm{g}$ was used to scale the entire modified profile ($I\mathrm{ag}(t)$), up or down as appropriate, to achieve the target plasma concentration without changing its shape. The new profile ($I\mathrm{n}(t)$) was derived as follows:

$$I\mathrm{n}(t) = I\mathrm{ag}(t) . F\mathrm{g} \qquad (2)$$

This new profile was administered to a further group of patients as the next iteration, and the process repeated until a profile with the desired characteristics was developed. Five iterations, in a total of 16 patients, were required to develop the profile used in this study and presented in table I.

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LATE POSTOPERATIVE EPISODIC AND CONSTANT HYPOXAEMIA AND ASSOCIATED ECG ABNORMALITIES

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SUMMARY

Twenty-two patients without cardiopulmonary disease and undergoing elective major abdominal surgery were monitored continuously with a Holter tape recorder and a pulse oximeter on one night before operation and the first two nights after operation (23:00 to 07:00), without oxygen therapy. Mean heart rate increased 16 beat min^{-1} *(*$P < 0.001$*) and mean oxygen saturation (*Sa_{O_2}*) decreased 2.6% (*$P < 0.001$*) after operation. Episodic oxygen desaturation to less than 80% occurred in four patients before operation, but in 13 patients after operation (*$P < 0.05$*). ECG abnormalities were observed in 10 patients before operation and in 16 patients after operation (ns). Individual maximum ST depression was more pronounced after than before operation (*$P < 0.05$*). Episodic desaturation was related closely to tachycardia in six patients before operation and one patient after operation; before operation to atrioventricular block in one patient, and after operation to ST depression in two patients. Mean* Sa_{O_2} *on the second night after operation correlated with total dose of opioid for pain relief (*$r_s = -0.48$*;* $P < 0.05$*), and postoperative decrease in* Sa_{O_2} *correlated with postoperative increase in heart rate (*$r_s = -0.43$*;* $P < 0.05$*). No patient had postoperative cardiac complications indicating treatment.*

KEY WORDS

Complications: postoperative hypoxaemia, arrhythmia. Monitoring: postoperative, electrocardiography, pulse oximetry.

Arterial hypoxaemia is common as either a constant or an episodic phenomenon following major surgery [1, 2]. Cardiac ischaemia and infarction (MI) occur also with increased frequency during the perioperative period, with peak incidences during operation and on the third day after operation [3, 4]. Although the pathogenesis of the late incidence is still debatable [3], our preliminary observations suggest that hypoxaemia may be a contributory factor [2].

The aim of the present study was to assess the relationship between hypoxaemia and cardiac function evaluated by continuous pulse oximetry and Holter monitoring before operation and in the late postoperative period.

MATERIALS AND METHODS

We studied 22 patients (12 men and 10 women, median age 70 yr (range 44–79 yr), weight 73 (52–99) kg) undergoing major abdominal surgery. Six of the patients participated in our previous study [2]. Exclusion criteria were symptoms of neurological, cardiac or respiratory disease, including excessive daytime sleepiness. Oxygen treatment was not given during the first 48 h after surgery, other than a few hours in the recovery room. All patients were undergoing elective surgery with no recognized risk factors and they received routine postoperative care.

Seven patients underwent cholecystectomy, five colonic resection, three gastric resection, two colo-colostomy following Hartmann resection, two ileal resection, one jejuno-jejunostomy, one rectal excision and one exploratory laparotomy. All patients received diazepam 5–10 mg for premedication; anaesthesia was induced and maintained with thiopentone, midazolam, low-dose

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fentanyl, suxamethonium, pancuronium and nitrous oxide in oxygen. Postoperative analgesia comprised morphine or ketobemidone 5–10 mg i.m. on demand; opioid administration was monitored for the first 48 h after surgery. Sedative drugs and peripherally acting analgesics were not used.

Measurements were performed on one night before operation and the first two nights after operation. All patients completed at least 8 h of continuous monitoring on all nights (23:00 to 07:00); only these results were used in the analyses. Oxygen saturation was measured with a Nellcor N-200 or an Ohmeda 3700 pulse oximeter using a finger probe [5], with subsequent data printout on a chart recorder the following morning.

Holter monitoring was performed using an amplitude modulated, two-channel tape recorder, model ICR 7200 (Instruments for Cardiac Research, Liverpool, NY, U.S.A.), with primary signal verification using a monitor (Quadriscope 8034, S&W Medico Teknik A/S, Copenhagen). The frequency response was 0.05–100 Hz (−3 dB), and the tape speed 1 mm s^{-1}. Two separate bipolar leads were recorded, CM_5 from electrodes placed in the second right intercostal space close to the sternal bone and in the V_5 position, and a modified orthogonal y-lead from electrodes just to the left of the spinal column, one on the superior angle of the scapula and one above the iliac crest [6]. The recordings were analysed semi-automatically using computerized equipment (Arrhytmiamaster, Spacelabs Inc., Redmond, Wa, U.S.A.). All arrhythmic events detected during the automatic analysis were checked carefully from full records from both leads. The results of ST segment analysis were presented in 1-min graphs from each lead. All episodes of ST segment changes were verified by at least three ECG recordings of each episode (beginning, maximum and end of change). As the resolution of the ST segment analysis was limited to 1-min averages, possible association between episodic hypoxaemia and ST depression could be found only when hypoxaemic events lasted more than 1 min.

The study was approved by the local Ethics Committee. Wilcoxon's signed rank test, Spearman's rank correlation test and Friedman's two-way analysis by ranks were used for statistical analyses. Level of significance was chosen as $P < 0.05$.

RESULTS

Sudden desaturation was defined as a decrease in oxygen saturation of 5% or more within 2 min. These desaturations were classified into those with an end-point equal to or greater than 80% oxygen saturation (Sa_{O_2}) and those with an end-point less than 80%. The median number of desaturations of 5% or more with end-point equal to or greater than 80% was 8 (range 0–44) on the night before operation, 5 (0–60) on the first night after operation and 9 (0–99) on the second night (ns). Before operation, two patients (Nos 3 and 8) had one episode of sudden desaturation to less than 80%, and two patients (Nos 20 and 18) had four and five similar episodes, respectively, all lasting less than 1 min. After operation, five patients had one (No. 10), one (No. 15), two (No. 9), eight (No. 2) and 18 (No. 16) episodes on the first night, and on the second night after operation 12 patients had one (No. 1), one (No. 10), one (No. 11), two (No. 2), two (No. 14), three (No. 21), three (No. 15), five (No. 6), 10 (No. 12), 12 (No. 8), 21 (No. 16) and 38 (No. 17) episodes to less than 80% Sa_{O_2} ($P < 0.05$ compared with before operation). The majority of these episodes (78/140) lasted less than 1 min, 55 episodes lasted 2–5 min and seven episodes lasted 6–12 min.

The median decrease in Sa_{O_2} (fig. 1) was 2.1% on the first night after operation ($P < 0.001$), and 2.6% on the second night ($P < 0.001$) compared with preoperative values. Before operation the minimum Sa_{O_2} was 86% (median, range 72–90); it was 83% (67–91) on the first night after operation (ns) and 78% (60–89) on the second night ($P < 0.05$ compared with before operation).

The median increase in heart rate (fig. 1) was 20 beat min^{-1} on the first night after operation and 16 beat min^{-1} on the second night (both $P < 0.001$ compared with before operation). Maximum heart rate was 94 (87–121) beat min^{-1} on the night before operation, 102 (80–128) beat min^{-1} on the first night after operation and 102 (78–132) beat min^{-1} on the second night (both $P < 0.05$ compared with before operation) (medians and ranges).

Seven patients showed a close correlation between sudden desaturation and increase in heart rate (more than 10% increase from baseline) (fig. 2)—six on the night before operation (Nos 1, 2, 9, 10, 16 and 21) and one on the second night after operation (No. 12). Saturation did not decrease to less than 80% in any of these episodes, and none

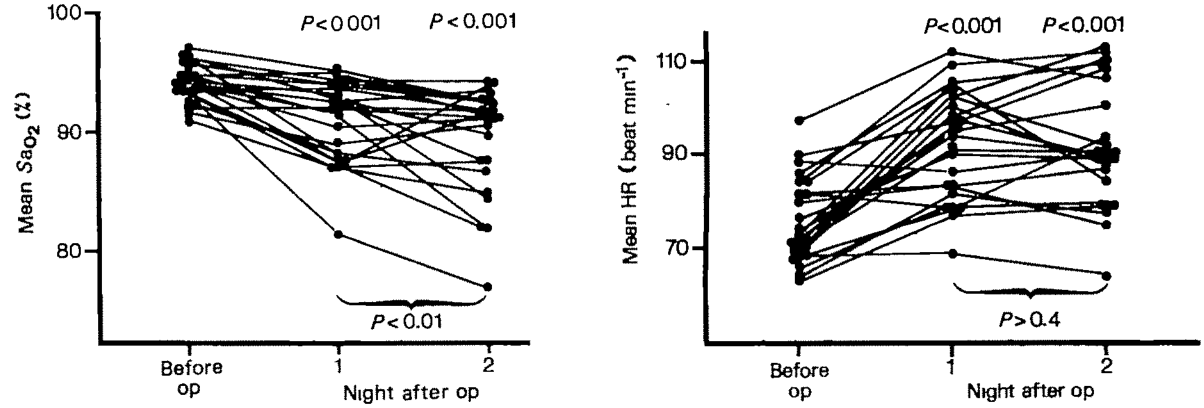

FIG. 1. Changes in mean oxygen saturation (Sa_{O_2}) and mean heart rate (HR) in 22 patients undergoing laparotomy (Friedman, $P < 0.001$).

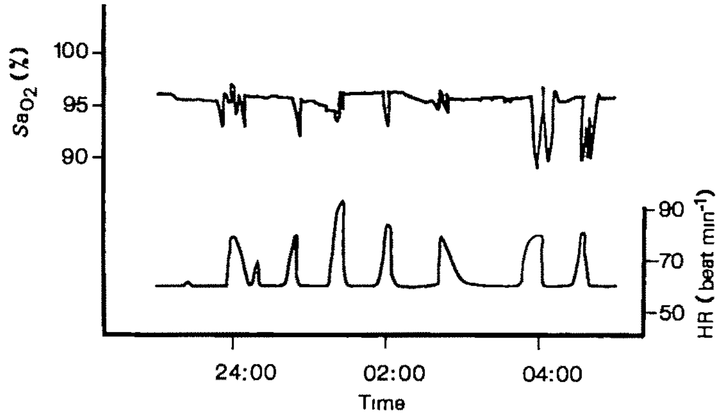

FIG. 2. Concomitant changes in Sa_{O_2} and heart rate (HR) in a patient on the night before surgery.

was associated with ST depression. Nine patients had a mean heart rate greater than 100 beat min⁻¹ (sinus tachycardia) on at least one night after operation, and two of these patients (Nos 4 and 17) had associated constant hypoxaemia (Sa_{O_2} = 87% and 82–77%, respectively). A weak correlation was found between increase in mean heart rate and decrease in mean saturation from before operation to the second night after operation (r_s = 0.43; $P < 0.05$).

Individual maximum ST depression was of significantly larger magnitude on the second night after operation (median −0.4, range −1.2 to 0) compared with before operation (median −0.2, range −1 to 0) ($P < 0.05$). Two patients (Nos 9 and 2) had episodes of ST depression lasting 30 and 70 min, respectively, accompanied by periods of episodic desaturation lasting 5 and 15 min on the first and second nights after operation, respectively (ST = −1.6 mm and −1 mm, Sa_{O_2} = 79% and 81%, repectively) (fig. 3). Two patients (Nos 14 and 22) had sinus tachycardia (HR = 105 and 103 beat min⁻¹) on the first night after operation associated with constant ST depression (ST = −1.2 mm and −1 mm), and the Sa_{O_2} values were 92% and 91%, respectively. One patient (No. 4) (fig. 4) had constant hypoxaemia on the second night after operation, when maximum ST depression and maximum heart rate occurred concomitantly (Sa_{O_2} = 85%, ST = −0.8 mm, HR = 120 beat min⁻¹).

Two patients (Nos 6 and 8) on the second night after operation had an index (number per hour) of ventricular extrasystoles (VPC) of 3 and 32, respectively, compared with an index of 1 and 1 before operation. Their mean Sa_{O_2} on the second night after operation were 82% and 85%, respectively. Three patients (Nos 8, 12 and 16) had VPC indexes on the first night after operation of 55, 14 and 5, respectively, and their mean Sa_{O_2}

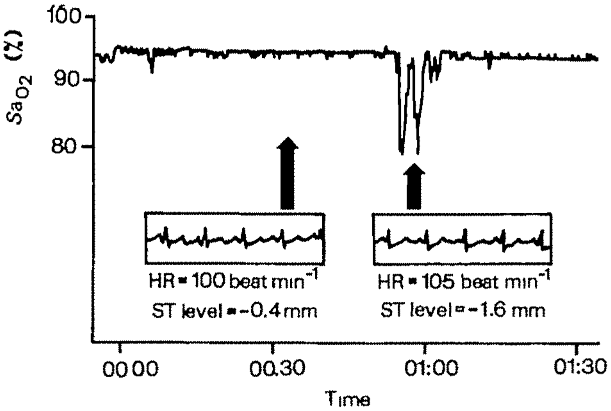

FIG. 3. Changes in Sa_{O_2} and ST level in a 71-yr-old man undergoing cholecystectomy; first night after operation. HR = Heart rate.

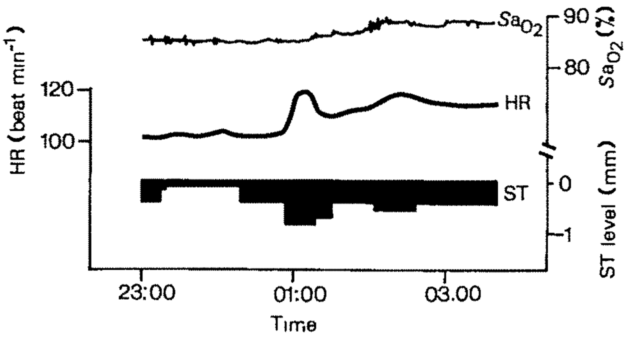

FIG. 4. Concomitant changes in Sa_{O_2}, heart rate (HR) and ST level in a patient undergoing jejuno–jejunostomy; second night after operation.

were all 87 % on this night. One patient (No. 18) had severe episodic desaturation (Sa_{O_2} 75 %) in the morning of the day before operation coinciding with second degree Mobitz type II atrioventricular block with a pause of 1.8 s (fig. 5).

Of postoperative cardiac events *not* related to changes in oxygen saturation, two patients (Nos 5 and 9) showed inverted diurnal heart rate (increased heart rate at night) on the second night after operation, and two patients (Nos 5 and 21) had VPC indexes of 12 and 183 on the second night after operation compared with preoperative indexes of 2 and 18, respectively. One patient (No. 10) had a VPC index on the first night after operation of 7, compared with 0 before the operation. On the night before operation three patients (Nos 7, 11 and 12) showed episodes of sinus arrest (2.4 s), accelerated idioventricular rhythm (8 beats) and ventricular tachycardia (4 beats), respectively.

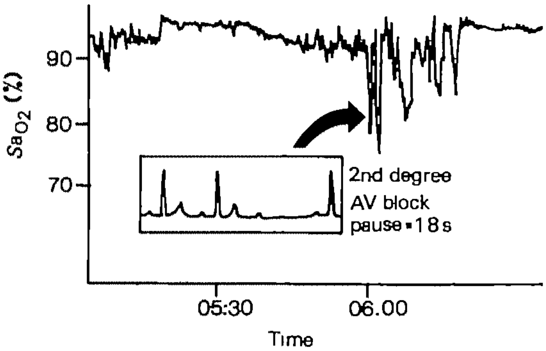

FIG. 5. Episodic oxygen desaturation with a concomitant atrioventricular block on the night before operation

Thus ECG abnormalities occurred in 18 of the 22 patients, of whom 16 developed *new* ECG abnormalities in the postoperative period (table I), while 10 had ECG abnormalities before

TABLE I. *Cardiac dysfunction and hypoxaemic events in patients undergoing abdominal surgery. Numbers in parentheses indicate the night after operation. †Episodic desaturation of 5% or more but not less than 80% oxygen saturation; ‡episodic desaturation of 5% or more with end-point less than 80% oxygen saturation; §closely related to episodic changes in oxygen saturation. Episodic desaturation is reported with the number of desaturations per night, with the corresponding code (night and † or ‡). Constant hypoxaemia is reported when mean saturation on the respective night (reported) was* $\leqslant 90\%$. *Episodic tachycardia is defined as a sudden short lasting (1–20 min) increase in heart rate of 10% or more. Sinus tachycardia is a mean heart rate greater than 100 beat* min^{-1} *on the respective night. ST depression is reported when maximum ST level was* $\leqslant -1$ *mm on the respective night. Ventricular extrasystoles (VPC) are included in the table if the index (number per hour) increased or decreased* $\geqslant 300\%$ *after surgery.* *$P < 0.05$*, sign test*

Patient No.	Preoperative cardiac dysfunction	Preoperative hypoxaemic events	Postoperative cardiac dysfunction	Postoperative hypoxaemic events
1	Episodic tachycardia§ ST depression VPC (index = 10)	Episodic hypoxaemia (†:7)	VPC (1:index = 2, 2:index = 2)	Episodic hypoxaemia (1†:9, 2‡:1, 2†:9)
2	Episodic tachycardia§	Episodic hypoxaemia (†:23)	ST depression§ (2)	Constant hypoxaemia (1:88%) Episodic hypoxaemia (1‡:8, 1†:60, 2‡:2, 2†:30)
3	—	Episodic hypoxaemia (†:23, ‡:1)	—	Episodic hypoxaemia (1†:4, 2†:2)
4	—	Episodic hypoxaemia (†:2)	Sinus tachycardia (2)	Constant hypoxaemia (1:87%, 2:87%) Episodic hypoxaemia (1†:4, 2†:5)
5	VPC (index = 2)	Episodic hypoxaemia (†:32)	Inversed diurnal heart rate VPC (1:index = 1, 2:index = 12)	Episodic hypoxaemia (1†:17, 2†:27)
6	VPC (index = 1)	Episodic hypoxaemia (†:1)	VPC (1:index = 1, 2:index = 3)	Constant hypoxaemia (2:82%) Episodic hypoxaemia (2‡:5, 2†:4)
7	Sinus arrest	Episodic hypoxaemia (†:4)	Sinus tachycardia (2)	Constant hypoxaemia (1:89%) Episodic hypoxaemia (1†:15, 2†:3)
8	VPC (index = 1)	Episodic hypoxaemia (†:25, ‡:1)	VPC (1:index = 55, 2:index = 32)	Constant hypoxaemia (1:87%, 2:85%) Episodic hypoxaemia (2‡:12, 2†:15)
9	Episodic tachycardia§	Episodic hypoxaemia (†:19)	Sinus tachycardia (2) Inversed diurnal heart rate ST depression (1§, 2)	Episodic hypoxaemia (1‡:2, 1†:12, 2†:1)
10	Episodic tachycardia§ VPC (index = 0)	Episodic hypoxaemia (†:32)	VPC (1:index = 4, 2:index = 0)	Episodic hypoxaemia (1‡:1, 1†:9, 2‡:1, 2†:7)
11	Accelerated idioventricular rhythm VPC (index = 185)	Episodic hypoxaemia (†:1)	VPC (1:index = 8, 2:index = 6)	Constant hypoxaemia (2:87%) Episodic hypoxaemia (2‡:1, 2†:28)
12	Ventricular tachycardia VPC (index = 0)	Episodic hypoxaemia (†:7)	Episodic tachycardia§ (2) VPC (1:index = 8, 2:index = 0)	Constant hypoxaemia (1:87%, 2:82%) Episodic hypoxaemia (2‡:10, 2†:9)
13	—	Episodic hypoxaemia (†:1)	Sinus tachycardia (1)	Episodic hypoxaemia (2†:5)

14	—	Episodic hypoxaemia (†:44)	Sinus tachycardia (1) ST depression (1)	Constant hypoxaemia (2:90%) Episodic hypoxaemia (2‡:2, 2†:50)
15	—	Episodic hypoxaemia (†:3)	—	Constant hypoxaemia (1:88%, 2:87%) Episodic hypoxaemia (1‡:1, 1†:6, 2‡:3, 2†:27)
16	Episodic tachycardia§ Atrial fibrillation VPC (index = 0)	Episodic hypoxaemia (†:9)	Atrial fibrillation (1, 2) VPC (1:index = 5, 2:index = 0)	Constant hypoxaemia (1:87%) Episodic hypoxaemia (1‡:18, 1†:51, 2‡:21, 2†:99)
17	—	Episodic hypoxaemia (†:4)	Sinus tachycardia (1, 2)	Constant hypoxaemia (1:82%, 2:77%) Episodic hypoxaemia (2‡:38, 2†:38)
18	Second degree AV block§	Episodic hypoxaemia (‡:5, †:39)	Sinus tachycardia (1, 2)	Episodic hypoxaemia (2†:2)
19	—	Episodic hypoxaemia (†:2)	—	—
20	—	Episodic hypoxaemia (‡:4, †:22)	—	Episodic hypoxaemia (1†:10, 2†:1)
21	Episodic tachycardia§ VPC (index = 18)	Episodic hypoxaemia (†:43)	Sinus tachycardia (1, 2) VPC (1:index = 195, 2:index = 183)	Episodic hypoxaemia (1†:5, 2‡:3, 2†:28)
22	—	—	Sinus tachycardia (1) ST depression (1)	Episodic hypoxaemia (1†:10, 2†:28)
Totals	Constant hypoxaemia	0/22	Constant hypoxaemia	11/22, 1:8/22, 2:8/22*
	Episodic hypoxaemia†	21/22	Episodic hypoxaemia†	21/22, 1:13/22, 2:21/22
	Episodic hypoxaemia‡	4/22	Episodic hypoxaemia‡	13/22, 1:5/22, 2:12/22*
	Sinus tachycardia	0/22	Sinus tachycardia	9/22, 1:6/22, 2:6/22*
	ST depression	1/22	ST depression	4/22
	Inversed diurnal heart rate	0/22	Inversed diurnal heart rate	2/22
	Sinus arrest	1/22	Sinus arrest	0/22
	Accelerated idioventricular rhythm	1/22	Accelerated idioventricular rhythm	0/22
	Ventricular tachycardia	1/22	Ventricular tachycardia	0/22
	Preoperative increased VPC (see legend)	2/22	Postoperative increased VPC (see legend)	7/22
	Tachycardia related to episodic hypoxaemia	6/22	Tachycardia related to episodic hypoxaemia	1/22
	ST depression related to episodic hypoxaemia	0/22	ST depression related to episodic hypoxaemia	2/22
	AV block related to episodic hypoxaemia	1/22	AV block related to episodic hypoxaemia	0/22
	Tachycardia associated with constant hypoxaemia	0/22	Tachycardia associated with constant hypoxaemia	2/22
	VPC associated with constant hypoxaemia	0/22	VPC associated with constant hypoxaemia	4/22
	Patients with cardiac dysfunction		Patients with cardiac dysfunction	
	Total	10/22	Total	16/22
	Related to episodic hypoxaemia	7/22	Related to episodic hypoxaemia	3/22
	Related to constant hypoxaemia	0/22	Related to constant hypoxaemia	6/22*

operation which did not occur after operation. Of cardiac events related to episodic hypoxaemia, seven patients showed tachycardia (six before operation, one after operation), two patients developed ST depression (both after operation) and one patient an atrioventricular block (before operation). Of cardiac events related to constant hypoxaemia ($Sa_{O_2} \leqslant 90\%$), two patients exhibited tachycardia and four patients had increased ventricular premature contractions compared with non-hypoxaemic nights.

Pneumonia occurred in one patient (No. 8); none of the patients had cardiac dysfunction requiring treatment, and all wounds healed normally.

During operation, the patients received fentanyl 0.55 (0.2–1.3) mg and after operation opioid 20 (5–33) mg (morphine equivalents) on the first day after operation, 23 (0–55) mg on the second day and 44 (13–63) mg on the two days together (medians and ranges). There was no correlation between amount of opioid used and the number of sudden desaturations (ns). There was no apparent relation between the time of administration of opioid and appearance of heart rate and saturation disturbances. A weak correlation was found between total dose of opioid in the two days after operation and the mean Sa_{O_2} on the second night after operation ($r_s = -0.48$; $P < 0.05$).

DISCUSSION

Hypoxaemia is a common phenomenon following major surgery [2]. The pathogenesis of constant postoperative hypoxaemia is reduction in functional residual capacity leading to increased shunting of blood through the lungs [7], whereas sudden oxygen desaturation in the late postoperative period may be caused by an effect of opioids on ventilatory pattern [8] or disturbed postoperative sleep pattern [9]. We cannot exclude the possibility that cardiac effects could initiate changes in Sa_{O_2}, but consider it less likely.

Myocardial ischaemia and infarction occur with a peak incidence during operation and on the third day after operation [3, 10], the latter usually being the period with the least arterial oxygen content [1]. Our results, showing late postoperative myocardial ischaemia in patients without preoperative signs of cardiovascular disease, suggest that hypoxaemia and tachycardia may be involved in development of late postoperative myocardial ischaemia. Thus we found that myocardial ischaemia was related to episodic hypoxaemia in two patients (Nos 2 and 9), and to tachycardia in three patients (Nos 9, 14 and 22). Furthermore, the association between hypoxaemia and arrhythmias demonstrated in the intensive care setting [11] was confirmed in six of our patients (Nos 6, 8, 11, 12, 16 and 18). The clinical significance of a brief period of ischaemia in healthy patients is unknown, but experimental studies suggest that repeated episodes of ischaemia may have a cumulative effect and eventually cause myocardial infarction [12].

None of our patients complained of chest pain, in spite of cardiac ischaemia, but following major abdominal procedures it may be difficult to distinguish between surgical pain and pain resulting from myocardial ischaemia. Enzyme analyses were not performed in our patients.

Arrhythmias in healthy volunteers are thought to be of prognostic significance [13]. Perioperative studies on patients undergoing vascular surgery suggest that preoperative monitoring may optimize assessment of cardiac risk [14, 15], but in our small sample of patients without apparent cardiovascular disease, we were not able to confirm these results. Thus we did not find that preoperative arrhythmias or ischaemia were associated with postoperative cardiac ECG abnormalities, except in one patient (No. 21) in whom a preoperative VPC index of 18 was associated with marked postoperative increase in the VPC index.

Episodic hypoxaemia coincided with episodic tachycardia in seven patients. This may be a result of increased sympathetic output caused by desaturation leading to tachycardia [16, 17] and hypertension [18], or to an arousal response with tachycardia and lightening of the sleep phase [19, 20].

Treatment of episodic hypoxaemia in the late postoperative period has not been fully evaluated. Although episodic oxygen desaturation to less than 80% in the postanaesthetic recovery period may be eliminated by oxygen therapy ($FI_{O_2} = 28\%$) [21], episodic desaturation may still occur despite oxygen therapy for longer than the first day after operation [2].

Postoperative pain relief with extradural local anaesthetics in the early postoperative period was not associated with episodic oxygen desaturation, whereas i.v. infusion of morphine (loading dose range 6–47 mg) produced episodic oxygen desaturation to less than 80% in 10 of 16 patients in association with obstruction and hypoventilation [8]. Similar data are not available for the late postoperative period.

In conclusion, we have shown that episodic and constant hypoxaemia may be associated with myocardial ischaemia and arrhythmias in patients without apparent cardiovascular disease following elective uncomplicated abdominal surgery. Similar changes may be important in patients with pre-existing cardiac disease.

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ARE MYOTONIAS AND PERIODIC PARALYSES ASSOCIATED WITH SUSCEPTIBILITY TO MALIGNANT HYPERTHERMIA?

F. LEHMANN-HORN AND P. A. IAIZZO

SUMMARY

Excised muscles from patients with myotonia or periodic paralysis were subjected to the in vitro *contracture test for susceptibility to malignant hyperthermia (MH). In a group of 44 patients, this standard test gave four positive, 10 equivocal and 30 negative results. The results for 27 control muscles from normal subjects were negative. When the test was performed with less than normal concentrations of contracture-triggering substances (caffeine $\leqslant 2$ mmol litre^{-1}, $\leqslant 2\%$ halothane), 70% of the muscles from the patients and only 15% of the controls responded with small contractures (< 0.2 g). These results should not be taken to indicate that the patients have the genetic trait for MH. The positive and equivocal test results, in addition to the slight contractures, may be accounted for by the electrical after-activity in the cases of pure myotonia, and by increased resting myoplasmic [Ca^{2+}] in myotonic dystrophy. This shows that the* in vitro *contracture test lacks specificity.*

KEY WORDS

Complications: myotonia, periodic paralysis. Hyperthermia, malignant: in vitro *contracture test.*

Events similar to malignant hyperthermia (MH) may occur in patients with myotonia when they are exposed to volatile anaesthetics [1–11]. Moreover, depolarizing neuromuscular blocking drugs may cause masseter spasm or generalized muscle spasms in these patients and thus affect tracheal intubation or ventilation [1, 12–22]. When such incidents occur, it is important to ascertain if the patient is a genetic carrier of the trait of MH. The only generally accepted test for this is the *in vitro* contracture test. This standard test determines the sensitivity of excised muscle bundles to separately administered caffeine and halothane; muscles from persons susceptible to MH have lower contracture thresholds for these agents than normal muscle.

Although a clearly positive result (contractures during *in vitro* exposure of muscle bundles to caffeine $\leqslant 2$ mmol litre^{-1} and $\leqslant 2\%$ halothane) has never been reported for patients with any form of myotonia, an association between myotonia and MH seems possible, as the threshold concentrations of caffeine [3] or halothane [14, 15] for induction of muscle contractures have been reported to be reduced. To study this possibility, we have compared the caffeine and halothane thresholds of muscles from myotonic patients with those of normal muscle. A few patients with periodic paralysis were available also for this study. In selected subjects, we tested also the effect of a depolarizing agent, suxamethonium, on the excised muscles or measured the myoplasmic Ca^{2+} concentration during muscle rest, in order to obtain more insight into the mechanisms underlying abnormal results.

PATIENTS AND METHODS

Bundles of intact fibres or fibre segments were dissected from muscle biopsies obtained from normal control patients and from patients with one of the following disorders with symptoms of myotonia or periodic paralysis: recessive generalized myotonia [23]; myotonia congenita;

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Schwartz–Jampel syndrome; myotonic dystrophy [23]; hyperkalaemic periodic paralysis [24]; hypokalaemic periodic paralysis; and thyrotoxic periodic paralysis. The stage, distribution and specific characteristics of the disease were evaluated in each patient by electromyography and quantitative force measurements on several muscle groups. The diagnoses were verified by assessing the effects of exercise, K^+ load, glucose and insulin load, or peripheral cooling. As the patients and their diagnoses have been described previously in detail [23, 24], we have given them the same numbers as before to facilitate cross-reference.

Fibre segments $\geqslant 3$ cm long were dissected under local anaesthesia from the motor point region of muscles showing myotonia or episodes of weakness (vastus lateralis, vastus medialis, biceps brachii, deltoid or tibialis anterior muscles). One patient with Schwartz–Jampel syndrome and 21 control patients who had to undergo thoracic surgery consented to biopsy of intact intercostal fibres (approximately 1.5 cm long) or specimens of fibre segments (about 3 cm long) from their latissimus dorsi. Fibre segments were taken also from the vastus lateralis muscle of six healthy volunteers. All procedures were performed in accordance with the Helsinki convention and approved by the Ethics Committee of the Technical University of Munich.

The excised muscle specimens were transported to the laboratory in a standard solution (composition given below). The solution was at room temperature and was gassed continuously with carbogen (5% carbon dioxide in oxygen). Bundles of muscle fibres were dissected with a diameter of approximately 2 mm. Up to four bundles were mounted in parallel experimental chambers and stimulated at 0.1 Hz with supramaximal pulses of 1 ms duration. Each bundle was stretched until the twitch amplitude was maximal. At this length, slight shortening or lengthening did not alter the force amplitude. The static version of the test protocol supported by the European Malignant Hyperpyrexia Group (EMHG) [25] was followed strictly, with the exception that muscles other than the vastus were used also. The force records were evaluated according to the criteria of this protocol. The baseline for contractures was defined as the force level just before addition of the smallest concentration of a drug. Twitch relaxation was defined as "slowed" when a noticeable fraction of force remained between twitches stimulated at the rate of 0.1 Hz. All tests were completed within 5 h after biopsy.

The standard solution contained (mmol litre^{-1}): NaCl 118.2, KCl 3.4, $MgSO_4$ 0.8, $CaCl_2$ 2.5, KH_2PO_4 1.2, $NaHCO_3$ 25.0, and glucose 5.5 (315 mosmol litre^{-1}). The pH of the carbogen-gassed solution was 7.4, the temperature 37 °C. Halothane was bubbled through the bath via a halothane vaporizer (Vapor, Dräger, Lübeck, FRG). The concentration of halothane was monitored with a digital sensor (Iris, Dräger, Lübeck, FRG). The rate of bubbling was controlled by two Teflon flow meters (ROTA Apparate, FRG). The concentration of halothane in the bath was determined by gas chromatography [26]. Caffeine (dehydrated; Carl Roth, Karlsruhe, FRG) was added cumulatively to the bath to produce final concentrations of 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0 and 32 mmol litre^{-1}. As any slight mechanical stimulation (e.g. movements caused by gassing of the solution) may induce electrical activity in myotonic muscle, tetrodotoxin 1 μmol litre^{-1} was added to the bath for suppression of action potentials when required. In some cases, the bundles were exposed also to suxamethonium (Lysthenon 2%, Hormon-Chemie, Munich, FRG). The agent was dissolved in water and was added directly to the bath so that the final concentration was 1.1 mmol litre^{-1}.

Myoplasmic [Ca^{2+}] was estimated in thin sheets of resealed fibre segments by means of fura-2 while isometric force was monitored simultaneously with a strain gauge (Akers, Horton, Norway). The methodology was exactly as described elsewhere [27].

RESULTS

The *in vitro* contracture test is considered positive when the bundles produce sustained contractures with amplitudes $\geqslant 0.2$ g during both application of caffeine $\leqslant 2.0$ mmol litre^{-1} and application of $\leqslant 2.0$% halothane. The result is equivocal when a contracture is elicited by only one test substance.

Within the patient group, 30 of the tests were negative, 10 equivocal and four positive; all muscles from the normal subjects gave negative results (fig. 1, table I). The four positive results were obtained for patients with myotonic dystrophy. In two of these muscles we determined also the resting myoplasmic [Ca^{2+}], which was increased (fig. 2, table II) [27]. In contrast, we found the resting [Ca^{2+}] normal in muscles from

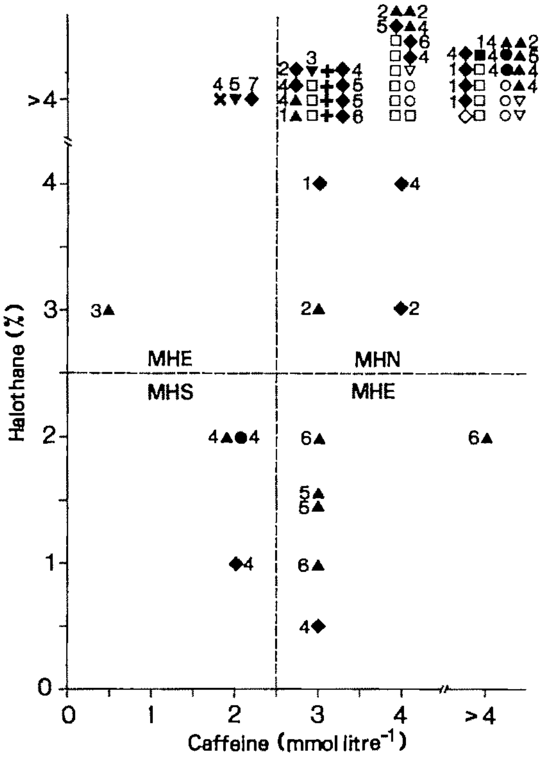

FIG. 1. Results obtained with the *in vitro* contracture test. Ordinate: concentration of halothane required for the induction of a contracture of ⩾ 0.2 g; abscissa: concentration of caffeine required for the same contracture amplitude. The dashed lines divide the plot into four regions designated [25]: malignant hyperthermia normal (MHN), malignant hyperthermia susceptible (MHS) and (two) malignant hyperthermia equivocal (MHE). The bundles used for the test were prepared from: cut intercostal (+), intact intercostal (□), biceps brachii (◇), latissimus dorsi (▽), tibialis anterior (×), vastus lateralis (○) and vastus medialis (△) muscles. Open symbols = controls: closed symbols = patients. Numbers next to symbols represent the various diseases: 1 = recessive generalized myotonia; 2 = myotonia congenita; 3 = Schwartz–Jampel syndrome; 4 = myotonic dystrophy; 5 = hyperkalaemic-, 6 = hypokalaemic- and 7 = thyrotoxic periodic paralysis.

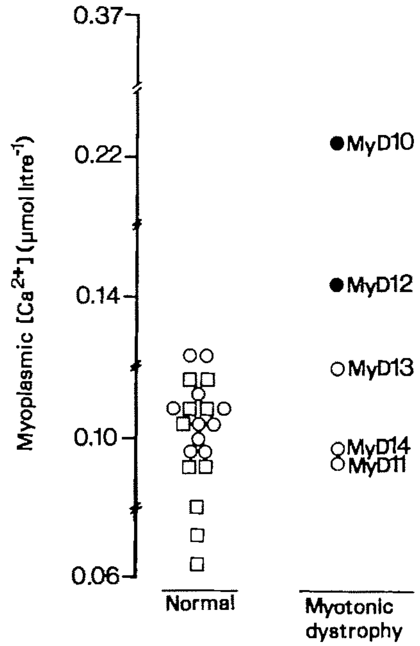

FIG. 2. Comparison of the myoplasmic Ca^{2+} concentration measured at rest in muscle fibres from normal subjects (left) and from five patients with myotonic dystrophy (right). Intact fibres (□) and long fibre segments (○) were studied. ● = Muscle fibres for which the contracture test had given a positive result.

TABLE I. *Summary of the* in vitro *contracture test results. RGMy = Recessive generalized myotonia; MyC = myotonia congenita; SJS = Schwartz–Jampel syndrome; MyD = myotonic dystrophy; HyperPP = hyperkalaemic periodic paralysis; HypoPP = hypokalaemic periodic paralysis; ThyrPP = thyrotoxic periodic paralysis. Hal. = ⩽ 2% Halothane; Caff. = caffeine ⩽ 2 mmol litre^{-1}*

					Small response		Slowed relaxation	
Disease	*n* (−)	Positive	Equivocal	Negative	Hal.	Caff.	Hal.	Caff.
RGMy	6	—	—	6	5	6	5	6
MyC	6	—	—	6	6	5	5	5
SJS	2	—	1	1	2	2	2	2
MyD	17	4	1	12	10	11	5	5
HyperPP	7	—	4	3	2	5	0	1
HypoPP	5	—	3	2	2	1	0	0
ThyrPP	1	—	1	—	0	1	0	0
Totals	44	4	10	30	27	31	17	19
Normal	27	—	—	27	4	4	0	0

TABLE II. *Additional findings for the patients who had positive or equivocal test results. SJS = Schwartz–Jampel syndrome; MyD = myotonic dystrophy; HyperPP = hyperkalaemic periodic paralysis; HypoPP = hypokalaemic periodic paralysis; ThyrPP = thyrotoxic periodic paralysis. †Severity of disease rated 1–5, with a score of 5 indicating severe affliction (e.g. wheelchair bound). §No permanent weakness, but periodic attacks (approximately 1/month). *Positive* in vitro *reactions to suxamethonium. ‡Increased* $[Ca^{2+}]$

Patient	Severity†	Test	Muscle	Morphology
SJS2	4	Equivocal	Vastus	Hypertrophic fibres, central nuclei
MyD2	3	Equivocal	Tibialis anterior	Moderate myopathy, sarcoplasmic masses
MyD5	3	Positive	Vastus	Slight myopathy, increased nuclei, slight interstitial changes
MyD10	3	Positive‡	Vastus	Moderate myopathy, slight neuropathy, increased nuclei, slight type grouping
MyD12	3	Positive‡	Biceps	Slight myopathy, slight neuropathy, increased nuclei, sarcoplasmic masses
MyD20	2	Positive	Biceps	Advanced myopathy
HyperPP5	2	Equivocal	Latissimus dorsi	Slight myopathy, vacuoles
HyperPP7*	2	Equivocal	Vastus	Slight myopathy, numerous vacuoles
HyperPP8*	2	Equivocal	Vastus	Slight myopathy, tubular aggregates
HyperPP9	2	Equivocal	Biceps	Moderate myopathy, tubular aggregates
HypoPP8	1§	Equivocal	Vastus	Normal
HypoPP10	2	Equivocal	Vastus	Vacuoles
HypoPP11	4	Equivocal	Vastus	Severe neuropathy, moderate secondary myopathy
ThyrPP1	2	Equivocal	Biceps	Slight calibre changes, type II atrophy

three patients with myotonic dystrophy (fig. 2) and two patients with recessive generalized myotonia who had negative results with the contracture test.

Small contractures (< 0.2 g) in response to low concentrations of halothane ($\leqslant 2.0\,\%$) or caffeine ($\leqslant 2.0$ mmol litre^{-1}) were provoked in up to 70 % of the muscles from the patient group (table I). This type of response, which is not considered relevant by the EMHG, appeared in only 15 % of the records from normal subjects. In MH negative subjects having a family member known to be susceptible to MH, this percentage is 23 % ($n = 35$) [own unpublished observations].

Slowed twitch relaxation (see Methods) was observed in most bundles obtained from patients with myotonia [23]. In the presence of caffeine or halothane, the remaining force increased. The remaining force was the greatest in muscles from those patients in whom myotonia was detected most readily *in vivo* (in EMG); these were the patients with recessive generalized myotonia, myotonia congenita, or Schwartz–Jampel syndrome (table I). Slowed twitch relaxation in the presence of caffeine or halothane was observed also in muscles from five of 17 myotonic dystrophy patients. In muscles from the 13 patients with periodic paralysis, only three with slowed relaxation were noted when the fibres were exposed to very high concentrations of halothane ($\geqslant 4\,\%$) or caffeine ($\geqslant 4$ mmol litre^{-1}).

Suxamethonium 1.1 mmol litre^{-1} readily induced contractures $\geqslant 0.1$ g in the fibre segments from patients with myotonia (fig. 3c). In contrast, on fibre bundles from normal muscle ($n = 12$) and from patients with hypokalaemic periodic paralysis ($n = 2$), the agent did not cause contractures, in spite of the fact that they contained endplates as verified visually [15]. The following is a summary of the positive responses to administration of suxamethonium: recessive generalized myotonia, 100 % ($n = 3$); myotonia congenita, 50 % ($n = 6$); Schwartz–Jampel syndrome, 100 % ($n = 1$); myotonic dystrophy, 70 % ($n = 7$); hyperkalaemic periodic paralysis with myotonia, 100 % ($n = 2$). The largest amplitudes (0.8 g) and the longest durations (120 s) were observed in contractures of fibres from patients in whom intense myotonic activity had been recorded both *in vivo* and *in vitro* (recessive generalized myotonia Nos 5, 6, 7 and Schwartz–Jampel syndrome No. 1) [23].

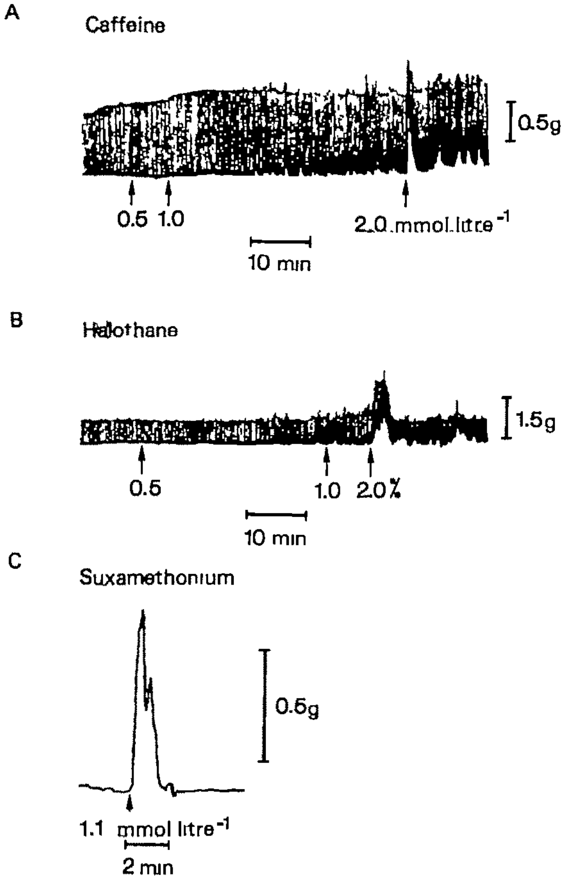

FIG. 3. Force records from muscles from patients with recessive generalized myotonia stimulated at 0.1 Hz with supramaximal pulses. A: Increasing concentrations of caffeine were added to the muscle bath, which led to abnormally slow relaxation of the twitches (recessive generalized myotonia patient No. 4). B: Similar results with halothane in the same patient. C: A contracture induced by suxamethonium (recessive generalized myotonia patient No. 7).

DISCUSSION

We did not obtain a positive or equivocal contracture test from any patient with pure (recessive generalized or congenital) myotonia. This supports results of similar studies on goats with congenital myotonia [28], but is in conflict with reports on patients with congenital myotonia with positive caffeine or halothane test results [3, 14, 15]. We did observe in the muscles of these patients, abnormally slowed relaxation which led to a type of contracture when the effect was increased by caffeine or halothane. This finding might explain the positive results mentioned above, but it does not seem related to pathologically increased reticular [Ca^{2+}] release, as are the contractures in MH. These pseudo-contractures are caused by the known myotonic abnormality of the sarcolemma—that is, the disturbed excitability. Contractions produced by electrical "after-activity" could, in severe cases, interfere with the contracture test. Thus it might be best to omit electrical stimulation when performing the *in vitro* contracture test with muscles from patients with pure myotonia.

The high incidence of positive or equivocal test results in muscles from patients with myotonic dystrophy may suggest that these patients possess the genetic trait for MH. The MH gene has been mapped recently on chromosome 19—the chromosome that codes also for the myotonic dystrophy (DM) gene [29], but the distance between the two genes is of the order of 25 cM, which makes it very unlikely that the two conditions are genetically linked.

Both MH episodes and progressive dystrophy are connected with an increased myoplasmic [Ca^{2+}] of the muscle, but via different pathomechanisms. In MH, the intracellular Ca^{2+} release is disturbed by the triggering agents [27], while in dystrophy the Ca^{2+} influx from the extracellular space is abnormally great [30]. Both mechanisms seem to generate a similar condition for the test. Our findings show that the test result may depend on the stage of the disease, that is, on how many fibres are affected and to what degree. The difference in mechanisms in MH and myotonic dystrophy is reflected also in the finding that muscles from patients susceptible to MH are rarely dystrophic [31]. We conclude from our results that the standard MH testing procedure lacks specificity.

A positive test result does not imply that anaesthetic complications must occur—not even in patients who are susceptible to MH [32]. In fact, neither our patients described here nor their family members are known to have had an event during anaesthesia which could be classified clearly as MH.

A muscle may have a normal sensitivity to halothane (or caffeine, or both), and may react abnormally to other agents. The myotonic reaction is known to be exaggerated by depolarizing neuromuscular blocking drugs [1, 12–22]. An increase in involuntary electrical after-activity is the most likely cause of this stiffness. This is consistent with our *in vitro* finding that suxamethonium-induced contractions occur in muscles from patients with myotonia, whereas no responses to suxamethonium were found in bundles from normal patients [33].

Although we conclude that the myotonias and periodic paralyses are not associated with susceptibility to MH, we should stress that the anaesthetist should be prepared for an anaesthetic-induced reaction in any of these patients and that non-triggering anaesthesia is indicated.

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EFFECT OF ISOFLURANE ON THE CANINE HEPATIC CIRCULATION AND HEPATIC OXYGEN BALANCE

C. D. MILLER, W. FITCH AND I. A. THOMSON

SUMMARY

We have studied the effects of increasing concentrations of isoflurane (1%, 1.5% and 2%) on the hepatic circulation and the oxygen supply and demand of the liver in six barbiturate-anaesthetized greyhounds. Following laparotomy, the hepatic arterial and portal venous blood flows were measured continuously using electromagnetic flow probes, and mean arterial pressure and cardiac output were measured as appropriate. Cardiac output was maintained while mean arterial pressure and systemic vascular resistance decreased in a dose dependent manner. Hepatic arterial and total liver blood flows and oxygen supplies decreased significantly at all isoflurane concentrations. Portal venous blood flow and portal venous oxygen supply did not decrease significantly until the concentration of isoflurane was increased to 2% and 1.5%, respectively. Hepatic oxygen consumption was reduced with 2% isoflurane ($P < 0.05$), but this was insufficient to offset the reduction in hepatic oxygen supply and resulted in an increased extraction of oxygen by the liver.

KEY WORDS

Anaesthetics, volatile: Isoflurane. Liver blood flow, oxygenation.

The unique dual blood supply to the liver provides a means by which hepatic blood flow and, hence, delivery of oxygen to the liver may be maintained under a variety of conditions. For example, a reciprocity of response has been shown between blood flow in the portal vein and that in the hepatic artery such that, when portal vein blood flow decreases, resistance in the hepatic artery decreases also and results in an increase in hepatic artery blood flow [1]. Consequently, oxygen supply to the liver is "protected"—at least under physiological conditions.

Although individual anaesthetic agents may have similar effects on total liver blood flow [2, 3], they may have differing effects on this reciprocity of response between the portal vein and the hepatic artery. For example, Hughes and colleagues [3] demonstrated that the resistance in the hepatic artery increased during administration of halothane, in association with a decrease in portal vein blood flow. In contrast, they observed that hepatic arterial resistance decreased during the administration of enflurane despite similar alterations in portal vein blood flow.

The present study in the anaesthetized greyhound was undertaken to assess the effects of increasing concentrations of isoflurane on blood flow to the liver and hepatic oxygen balance. In particular, we wished to characterize the effects of isoflurane on hepatic artery blood flow, portal vein blood flow and their relationship.

MATERIALS AND METHODS

Anaesthesia

Six greyhounds weighing between 20 and 35 kg were fasted overnight. Anaesthesia was induced with thiopentone 20 mg kg^{-1} i.v. and maintained with pentobarbitone 30 mg kg^{-1} i.v. Neuromuscular block was provided with pancuronium 0.15 mg kg^{-1} i.v. and, after tracheal intubation, the lungs were ventilated with a mixture of 75% nitrogen in oxygen at a rate of 14 b.p.m. with an inspiratory to expiratory ratio of 1:2. Minute

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volume and inspired oxygen concentration were adjusted to maintain normal values of Pa_{CO_2} and Pa_{O_2}.

Surgical preparation

Following laparotomy, the hepatic artery was dissected free of adventitia at a site 1–2 cm from the coeliac axis and a 3-mm electromagnetic flow probe (Stratham) was applied. During this procedure, care was taken to preserve the peri-arterial nerve plexus. The gastroduodenal and right gastric arteries were ligated to ensure that true hepatic artery flow was measured. The portal vein was dissected proximal to the insertion of the gastroduodenal vein and a 5-mm electromagnetic flow probe was applied.

The flow probes were connected to a pair of synchronized flow meters (Stratham SP 2202) which possessed an electronic zeroing facility. The portal vein was cannulated via a catheter placed in the gastroduodenal vein, and the hepatic vein via the external jugular vein. From these cannulae, portal venous and hepatic venous blood samples were obtained and venous pressures could be monitored. Hepatic oxygen supply and oxygen consumption were calculated from measurements of oxygen content in blood obtained from the femoral artery (equivalent to hepatic artery oxygen content), portal vein and hepatic vein (Lex-O_2-Con electrolytic cell; Lexington Instruments) and inserted in the following equations:

Hepatic artery oxygen supply (ml min^{-1})

$$= \frac{\text{hepatic artery blood flow}}{100} \times \text{hepatic arterial oxygen content} \quad (1)$$

Portal vein oxygen supply (ml min^{-1})

$$= \frac{\text{portal vein blood flow}}{100} \times \text{portal venous oxygen content} \quad (2)$$

Hepatic oxygen consumption (ml min^{-1})

$$= \left[(\text{portal venous} - \text{hepatic venous oxygen content}) \times \frac{\text{portal vein blood flow}}{100}\right] + \left[(\text{hepatic arterial} - \text{hepatic venous oxygen content}) \times \frac{\text{hepatic artery blood flow}}{100}\right] \quad (3)$$

Hepatic oxygen extraction efficiency (%)

$$= \frac{\text{hepatic } O_2 \text{ consumption}}{\text{hepatic artery } O_2 \text{ supply} + \text{portal vein } O_2 \text{ supply}} \times 100 \quad (4)$$

Mean arterial pressure (MAP) was measured via a catheter inserted into the abdominal aorta via the femoral artery. Cardiac output (CO) was measured by the thermal dilution method, using a triple-lumen, thermistor-tipped, flow-directed catheter (Devices) placed in the pulmonary artery via a femoral vein. This catheter was used also to monitor core temperature, which was maintained at 38 °C using radiant heat lamps.

Systemic vascular resistance, hepatic arterial resistance and mesenteric vascular resistance were calculated using the following equations:

Systemic vascular resistance (SVR)

$$= \frac{\text{MAP (mm Hg)}}{\text{cardiac output (litre min}^{-1})}$$

Hepatic arterial resistance (HAR)

$$= \frac{\text{MAP} - \text{hepatic venous pressure (mm Hg)}}{\text{hepatic arterial blood flow (ml min}^{-1})}$$

Mesenteric vascular resistance (MVR)

$$= \frac{\text{MAP} - \text{portal venous pressure (mm Hg)}}{\text{portal venous blood flow (ml min}^{-1})}$$

Arterial blood-gas tensions and the acid–base status of the animals were measured intermittently (Corning 165 blood-gas/pH analyser). The normal canine compensated metabolic acidosis was maintained at a base excess no greater than 4 mmol litre^{-1} [4], by administering sodium bicarbonate, as required.

Physiological saline solution was infused i.v. at a rate of 5–15 ml kg^{-1} h^{-1} to replace loss of fluid; however, care was taken to maintain PCV greater than 40%. At the end of each investigation the liver was removed and weighed.

Experimental programme

Approximately 3 h after induction of anaesthesia, and after baseline (control) values had been determined, a Fluotec Mk 3 (Cyprane) temperature-compensated vaporizer, calibrated previously for isoflurane, was switched into the circuit.

Isoflurane 1% was given for 30 min, during which time hepatic artery blood flow (HABF), portal vein blood flow (PVBF) and MAP were

TABLE I. *Effect of three concentrations of isoflurane on mean arterial pressure, cardiac output, systemic vascular resistance, hepatic artery blood flow, portal vein blood flow, total liver blood flow, portal venous resistance, hepatic arterial resistance and mesenteric vascular resistance (mean (SEM)). Significant differences from control:* $^*P < 0.05$; $^{**}P < 0.01$

	Isoflurane concentrations (%)			
	0	1	1.5	2
Mean arterial pressure (mm Hg)	154 (9.0)	118 (14)**	94 (14)**	55 (11)**
Cardiac output (litre min^{-1} kg^{-1})	0.153 (0.014)	0.131 (0.012)	0.147 (0.011)	0.122 (0.014)*
Systemic vascular resistance (mm Hg litre^{-1} min^{-1})	38.8 (5.0)	28.5 (3.3)*	22.9 (2.7)**	15.7 (1.6)**
Hepatic artery blood flow (ml min^{-1}/100 g liver)	44.6 (6.7)	32.6 (3.7)*	30.1 (2.8)*	22.3 (2.4)**
Portal vein blood flow (ml min^{-1}/100 g liver)	90.8 (11.7)	81.0 (11.0)	77.6 (13.8)*	60.0 (12.4)**
Total liver blood flow (ml min^{-1}/100 g liver)	137.1 (9.9)	114.1 (8.8)*	108.7 (11.2)*	82.9 (13.1)**
Portal venous resistance (mm Hg ml^{-1} $\text{min}^{-1} \times 10^2$)	0.651 (0.079)	0.671 (0.103)	0.619 (0.110)	0.588 (0.186)
Hepatic arterial resistance (mm Hg ml^{-1} min^{-1})	0.622 (0.095)	0.650 (0.128)	0.542 (0.123)	0.369 (0.060)**
Mesenteric vascular resistance (mm Hg ml^{-1} min^{-1})	0.284 (0.022)	0 240 (0.022)	0.200 (0.018)**	0.145 (0.018)**

monitored continuously. Discrete measurements of these and the other derived indices under study were made before, and at the end of, this 30-min period, and repeated after 30 min exposure to 1.5 %, 2 % and 3 % isoflurane. Arterial blood was sampled when baseline control values had been determined and after each 30-min period of administration of isoflurane. Blood concentrations of isoflurane were determined using gas–liquid chromatography [5].

The results were analysed using a two-way analysis of variance. Each value was compared with the baseline measurements using Dunnett's test [6] for multiple comparison procedures. $P < 0.05$ was taken as the level of significance.

RESULTS

Results are given for inspired isoflurane concentrations of up to 2 %, as four of the greyhounds died after developing extreme hypotension and a low cardiac output during exposure to 3 % isoflurane.

Systemic circulation

The decreases in MAP and SVR were significant at each concentration of isoflurane. The decrease in CO did not achieve statistical significance until an inspired concentration of 2 % isoflurane was used (table I).

Hepatic circulation

The decreases in HABF and total liver blood flow (TLBF) were significant at all concentrations of isoflurane, and decreased to 50 % and 60 %, respectively, of control values when 2 % isoflurane was used. The decrease in PVBF did not achieve statistical significance until an inspired concentration of 2 % isoflurane was used, when the PVBF decreased to 66 % of control value (table I).

HAR did not decrease significantly until 2 % isoflurane was used, while the decrease in MVR became statistically significant when 1.5 % and 2 % isoflurane were used. Portal venous resistance was not altered significantly by these concentrations of isoflurane (table I).

Hepatic oxygen consumption

The decrease in hepatic arterial oxygen content, portal venous oxygen content and hepatic venous oxygen content were significant with 1.5 % and 2 % isoflurane (table II). Hepatic artery oxygen supply decreased significantly with all the isoflurane concentrations while the decrease in portal venous oxygen supply did not become significant until 1.5 % isoflurane was used. The reductions in HABF and PVBF and oxygen contents combined to produce a significant decrease in the total oxygen supply to the liver at all of the concentrations of isoflurane. The decrease in hepatic oxygen consumption became significant only

TABLE II. *Effect of three concentrations of isoflurane on hepatic artery oxygen supply, hepatic vein oxygen supply, total hepatic oxygen supply, hepatic oxygen consumption and hepatic oxygen extraction efficiency (mean (SEM)). Significant differences from control:* $*P < 0.05$; $**P < 0.01$

	Isoflurane concentrations (%)			
	0	1	1.5	2
Hepatic artery oxygen content (ml/dl blood)	23.0 (0.7)	22.0 (1.1)	20.3 (0.7)*	19.2 (0.7)**
Portal vein oxygen content (ml/dl blood)	19.5 (0.8)	18.1 (1.1)	16.3 (1.0)*	13.1 (1.3)**
Hepatic vein oxygen content (ml/dl blood)	16.4 (0.7)	15.8 (1.3)	12.4 (1.4)*	9.9 (1.8)**
Hepatic artery oxygen supply (ml min^{-1}/100 g liver)	10.69 (1.83)	7.25 (0.76)*	6.34 (0.75)**	4.49 (0.67)**
Portal vein oxygen supply (ml min^{-1}/100 g liver)	18.08 (1.76)	15.04 (2.48)	12.96 (2.57)**	8.52 (2.22)**
Total hepatic oxygen supply (ml min^{-1}/100 g liver)	28.8 (1.6)	22.3 (2.1)*	19.3 (2.2)**	13.0 (2.5)**
Hepatic oxygen consumption (ml min^{-1}/100 g liver)	5.6 (0.8)	4.2 (0.5)	4.4 (0.5)	4.0 (0.6)*
Hepatic oxygen extraction efficiency (%)	19.7 (3.1)	20.0 (3.3)	25.2 (4.8)	39.1 (9.7)*

when 2% isoflurane was used; this coincided with a larger decrease in the total hepatic oxygen supply, which resulted in a significant increase in the hepatic oxygen extraction efficiency (table II).

The arterial isoflurane concentrations (SEM) measured after each 30-min period of administration of isoflurane were 0, 4.86 (0.39), 7.73 (0.83) and 11.5 (0.5) ml dl^{-1} for inspired isoflurane concentrations of 0, 1%, 1.5% and 2%, respectively.

DISCUSSION

The liver is a vascular organ which receives about 25% of the cardiac output during physiological conditions. TLBF is derived from two sources, the portal vein and the hepatic artery. PVBF arises from the other splanchnic organs and, although it normally supplies about 66% of the TLBF, it is independent of hepatic control. HABF was thought initially to supply only the supporting structures of the liver such as the portal vein and the bile ducts; however, more recent observations support additional roles for the HABF. It is essential for the nutrition of the hepatic parenchyma, normally providing about 50% of its oxygen requirement. It also serves to hold TLBF constant by means of the hepatic arterial buffer response, which itself is regulated by an adenosine washout mechanism occurring within the liver [1]. This allows the HABF to vary between 12 and 50% of TLBF.

With the exception of ketamine [7, 8], all of the previously studied anaesthetic agents, both i.v. (thiopentone, Althesin, etomidate) [9] and inhalation (halothane, enflurane [3], methoxyflurane [10]) significantly decrease TLBF in a dose-dependent manner when given to surgically stressed animals. The present study demonstrates a similar pattern during administration of increasing concentrations of isoflurane. It is not valid to compare directly results from different studies. However, when studying this model, the extent of the decrease in TLBF produced by isoflurane (approximately 20% at 1 MAC) would appear to be less than that produced by halothane (approximately 30% at 1 MAC) or enflurane (approximately 35% at 1 MAC) [3]. The precise mechanism subserving these decreases in TLBF in the surgically stressed dog are probably multifactorial; however, it would be difficult to argue against the primacy of the close relationship between the observed decreases in MAP and those in TLBF. Juhl and Erner-Jenson [11] suggested that, in surgically stressed dogs, the decrease in CO associated with administration of halothane is the main determinant of the decrease in TLBF. However, the results of the present study would favour a direct relationship between MAP and TLBF as, although TLBF and MAP decreased progressively when the concentration of isoflurane was increased, CO changed significantly only in association with administration of the greatest concentration of isoflurane. These findings are similar to those of Gelman, Dillard and Bradley [12] who studied surgically stressed isoflurane-anaesthetized pigs.

Currently, it is accepted that, at least under physiological conditions, the flow of blood in the portal vein is the major intrinsic regulator of hepatic arterial resistance [1]. As a result, the amount of blood reaching the liver via the hepatic artery increases as the blood flow in the portal vein decreases, and *vice versa*. In the present study, the dose-dependent decreases in TLBF were the result of decreases in flow in both the portal vein and the hepatic artery. Although HAR did decrease significantly with 2% isoflurane, the degree of vasodilatation was insufficient to prevent a decrease in HABF and the amount of oxygen supplied via the hepatic artery (see below). In other words, the hepatic arterial buffer response was less effective when assessed during administration of the volatile anaesthetic agent than would have been the case under more physiological conditions. This point is highlighted by the findings of Gelman, Fowler and Smith [13] in chronically instrumented dogs in which no surgical procedure had been undertaken. These workers observed that there were statistically insignificant decreases (9% and 23%, respectively) in TLBF when the dogs were anaesthetized with 1 MAC (1.4%) and 2 MAC isoflurane in oxygen compared with the awake state. During anaesthesia, significant decreases in PVBF were offset by significant increases in HABF, thus maintaining TLBF and, presumably, hepatic oxygen delivery.

Although a knowledge of the changes in the total blood supply to the liver is important, particularly as far as the pharmocokinetics of drugs and hormones with a high hepatic extraction are concerned, physiologically, the hepatic oxygen supply depends not so much on total hepatic blood flow as on hepatic artery blood flow. As the hepatic artery can, if required, supply up to 65–70% of the oxygen requirement of the liver [14], the ratio of HABF to PVBF could have a more important role in securing the oxygen supply of the liver than total liver blood flow *per se*. As a result of the decreases in HABF mentioned previously, the total hepatic oxygen supply decreased significantly with each increase in concentration of isoflurane, and as the hepatic oxygen consumption did not decrease in parallel with the decrease in supply, the liver had to extract more oxygen from the blood in order to meet its requirement for oxygen.

It would seem reasonable to argue that there was not a critical decrease in oxygen supply: even at the greatest concentration of isoflurane the oxygen content of hepatic venous blood was 9.9 (1.8) ml/dl blood. However, this is an averaged value which could not provide evidence for, or against, a critical decrease in oxygen supply around the terminal hepatic venules [15]. As we did not undertake any biochemical assessment of parenchymal function, this question must remain unanswered.

Although the study by Gelman, Fowler and Smith [13] is interesting it is obviously of more immediate clinical interest to the anaesthetist to characterize the effect of the individual anaesthetic agent on the circulation and oxygen balance of the liver, in animals in which a surgical procedure (laparotomy) has been undertaken. It then becomes apparent that the changes induced by the administration of the anaesthetic agent, although significant statistically, are relatively modest compared with those produced by surgery *per se* [16]. In other words, the effects of anaesthetic agents have a modifying rather than a major role on the circulation to the liver and hepatic oxygen flux.

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NITROUS OXIDE ANTAGONIZES CNS STIMULATION BY LAUDANOSINE IN MICE

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SUMMARY

We have investigated whether nitrous oxide antagonizes or augments the CNS stimulant action of laudanosine in mice by comparing the mean convulsive doses (CD_{50} (SE)) of a control group and those following pretreatment with 65% nitrous oxide in oxygen for 20 and 180 min. Nitrous oxide significantly increased CD_{50} from 46.8 (1.4) mg kg^{-1} of control to 57.3 (1.3) mg kg^{-1} at 20 min and 53.5 (1.7) mg kg^{-1} at 180 min. The attenuation of the effect of nitrous oxide at 180 min, suggestive of possible partial drug tolerance, was not statistically significant. These findings indicate that nitrous oxide antagonizes the CNS stimulating action of laudanosine.

KEY WORDS

Anaesthetics, gases: nitrous oxide. Neuromuscular relaxants: atracurium. Complications: seizures, laudanosine. Potency, anaesthetic. ED_{50}

Depolarizing neuromuscular blocking drugs administered i.v. do not cross the blood–brain barrier, but may activate the electroencephalogram (EEG) in humans [1, 2] and laboratory animals [3, 4]. This indirect CNS effect is induced by increased proprioceptive afferent activity from intrafusal muscle fibres stimulated by the blocker [5], by pain arising from muscle damage induced by fasciculation, or by both [2]. Non-depolarizing neuromuscular blocking drugs do not induce such intra- and extra-fusal muscle fibre contractions and have neither direct nor indirect action on the EEG during halothane anaesthesia [1]. The exception to this statement is atracurium which, at physiological pH and temperature, undergoes rapid spontaneous Hofmann degradation and ester hydrolysis [6], and the major metabolite, laudanosine, possesses convulsant activity [7]. The introduction of atracurium into clinical practice has thus renewed interest in the CNS actions of laudanosine [8–11].

Nitrous oxide has been reported previously to possess both CNS excitant and depressant properties: CNS stimulation is evident as activation of reticular cell firing [12] and excitation of preganglionic sympathetic fibres [13], and CNS depression as decrease in amplitude of somatosensory evoked responses [14], prolongation of the latent period of the tail-flick response to radiant heat in rats [15], suppression of ease of induction of enflurane convulsions [14], and increase in convulsion threshold in amygdaloid-kindled cats [16]. An increase in lignocaine seizure threshold has also been reported in cats [17].

In the present study, we have attempted to reveal if the CNS effects of laudanosine are augmented or suppressed by nitrous oxide. In our pilot study we noted that the EEG actions of clinical doses of atracurium were subtle and EEG changes *per se* were not quantitatively measurable [18]. We have measured, therefore, the modification of the convulsion threshold dose of laudanosine by nitrous oxide.

MATERIALS AND METHODS

Male ICR mice weighing 18–30 g were used in the study, which was approved by the Institutional Committee on Animal Research. Seizure thresholds for laudanosine were measured and compared in three groups of mice: control group, not exposed to nitrous oxide, and second and third experimental groups, exposed to nitrous oxide for 20 min and 180 min, respectively.

All experiments were conducted in a Plexiglas anaesthesia box with a polyethylene hood per-

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mitting easy access to the animals. The total volume of the system was 10 litre. The concentration of oxygen in the box was monitored continuously using an oxygen monitor (Ohmeda 5120). After initial flushing with 100% oxygen, a total gas flow of 4 litre min^{-1} was delivered from calibrated flowmeters in order to maintain concentrations of 35% oxygen and 65% nitrogen (or 65% nitrous oxide) in the box. Mice were studied in groups of three to five. Laudanosine 0.3% in saline was injected i.p. in doses from 35 to 70 mg kg^{-1} with a 5-mg step interval in a volume of 20 ml kg^{-1}. Behavioural changes after administration of laudanosine were observed and the number of convulsing mice counted.

After the experiment, all mice were killed with an overdose of pentobarbitone and examined for intra-abdominal blood vessel injury. If this had occurred, the animal was excluded from further analysis.

Air temperature in the box was monitored using a temperature probe (Terumo) and maintained at 24 ± 1 °C with a heating lamp.

Laudanosine (Aldrich Chemical Co. Ltd) in saline was prepared by acidifying with hydrochloric acid 1 mol $litre^{-1}$ and buffering to pH 7.0 with sodium bicarbonate 1 mol $litre^{-1}$. The final concentration of 3 mg ml^{-1} was adjusted by adding saline. Drug-free solvent solution at the same pH was prepared also and tested in three mice.

The quantal observations of the dose and the associated response (convulsion yes/no) were analysed using an iterative computer program for non-linear regression analysis. By the method of maximum likelihood, the program estimates directly the parameters of the logistic function

$$P = D^s/(D^s + \mathrm{CD}_{50}{}^s)$$

where P = probability of a convulsive response; D = dose of laudanosine; s = an exponent defining the slope of the curve; CD_{50} = the dose of laudanosine that results in a 50% probability of response (ED_{50}). In addition to CD_{50} and slope, it calculates their respective standard error—a measure of the precision of the parameter estimate. Continuous probability curves of convulsive response *vs* dose of laudanosine were plotted successively for each of the three data sets. The CD_{50} and slope values were compared between the three groups by calculating 95% confidence limits [19].

The mean time for onset of convulsions following administration of laudanosine was compared between the three groups by ANOVA [20].

RESULTS

Nitrous oxide increased the convulsive threshold dose of laudanosine in mice: CD_{50} of the 20-min nitrous oxide-treated group (57.3 (1.3) mg kg^{-1}) was significantly greater than CD_{50} of the control group (46.8 (1.4) mg kg^{-1}) (table I, fig. 1). The anticonvulsive effect of nitrous oxide was maintained for 180 min and CD_{50} of the 180-min nitrous oxide-treated group (53.5 (1.7) mg kg^{-1}) remained significantly greater than CD_{50} of the control group ($P < 0.05$). With time, there was a tendency for attenuation of the anticonvulsive action of nitrous oxide, and CD_{50} at 180 min was less than CD_{50} at 20 min (ns).

The behavioural changes after i.p. injection of laudanosine were dose-dependent and appeared rapidly. The initial phase was characterized by immobilization, grooming and wet-shake behaviour. This was followed by tremor, jerky movements and, finally, generalized convulsions with hind limb and tail extensions. The convulsions appeared at 201 (39), 202 (43) and 206 (62) s after administration of laudanosine in the control, 20-min and 180-min nitrous oxide pretreated groups, respectively. There were no significant differences between the three groups in the onset time of convulsions. The duration of convulsions and death rate were dose-dependent and, at a dose greater than the 100% convulsive dose in the control group, all mice died. When the

TABLE I. *CD_{50} (SE) and slopes (SE) of the laudanosine dose–effect curves for three different treatment groups. CD_{50} = Dose of laudanosine at which there is 50% chance of a convulsive response. 95% CL = 95% confidence interval ($\mathrm{CD}_{50} \pm t_{0.95,n-2} \times SE$). * Significantly different from control* ($P < 0.05$)

Treatment group	CD_{50} (mg kg^{-1})	95% CL (mg kg^{-1})	Slope	*n*
N_2/O_2 (20 min)	46.8 (1.4)	44.1–49.5	12.2 (2.9)	62
N_2O/O_2 (20 min)	57.3 (1.3)	54.7–59.9*	18.4 (4.9)	50
N_2O/O_2 (180 min)	53.5 (1.7)	50.1–56.9*	12.6 (3.6)	45

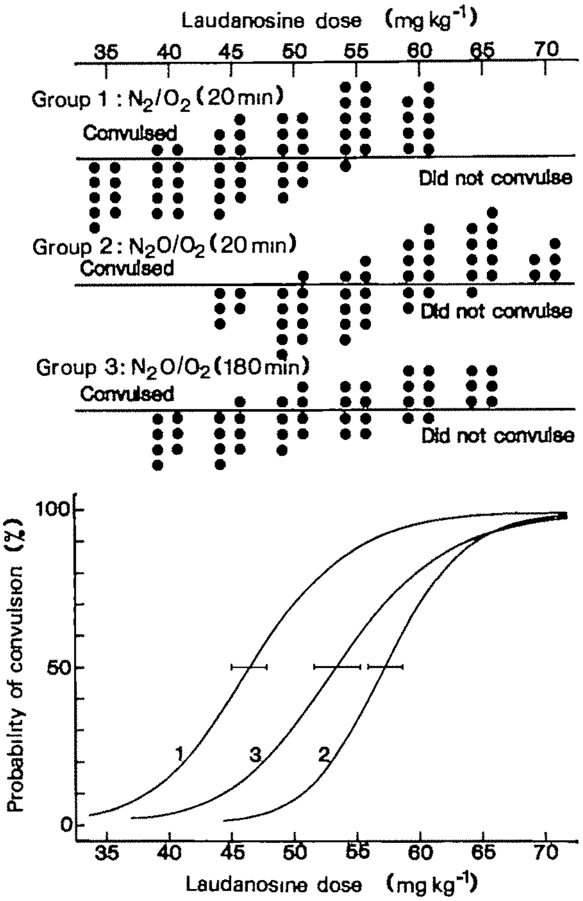

FIG. 1. Laudanosine dose–effect data for three different groups of mice. Upper diagrams: individual responses to different doses of laudanosine in each group. Graph: dose–effect curves derived from the quantal data using non-linear logistic regression. Horizontal bars indicate SE of CD_{50} (see table I).

pro-convulsive behavioural changes did not culminate in generalized seizure, the mice resumed normal activity after 10–15 min. In seven mice, intra-abdominal bleeding was found and they were excluded from further analysis.

A dose of vehicle solution given to three mice did not induce any noticeable changes.

DISCUSSION

The present study has demonstrated that nitrous oxide had a significant antagonizing effect on the convulsant action of laudanosine. Extrapolation of this finding to the clinical situation requires examination of the nature of the CNS actions of subconvulsive doses of laudanosine. We reported previously that, although all convulsants induced a marked increase in CNS cell firing at the stage of convulsion, the CNS actions of subconvulsive doses differed: for example, enflurane suppressed reticular cell firing at preconvulsive anaesthetic state [12, 21], while bicuculline, a GABA receptor antagonist, induced activation [22]. Moreover, multiphasic actions of suppression and activation were induced by subconvulsive doses of lignocaine [23]. A convulsant property of nitrous oxide has also been postulated [24]. These reports suggest that the CNS actions of subconvulsive concentrations of laudanosine are not necessarily excitatory. Nevertheless, there are some suggestions from previous reports which indicate an excitatory nature of clinical (subconvulsive) doses of laudanosine, such as "awakening" from anaesthesia [11, 25], activation of the EEG [26], and increase in the MAC value for halothane [10]. Therefore, both convulsant and subconvulsant doses of laudanosine are excitatory. This supports extrapolation of the present findings with convulsant doses of laudanosine to the effect on clinical (subconvulsive) doses of laudanosine. To our knowledge, the present study is the first to suggest that nitrous oxide in clinical doses has an antagonistic effect on CNS stimulation by laudanosine. This effect may be attributed to the CNS depressant actions of nitrous oxide.

There is considerable difference between the convulsive doses of laudanosine and those measured following administration of atracurium in clinical practice [4]. In humans receiving infusions of paralysing doses of atracurium, peak plasma concentrations of laudanosine up to 0.81 μg ml^{-1} have been measured at the end of surgery [25]. Much greater plasma concentrations of laudanosine, exceeding 17 μg ml^{-1}, were needed for convulsions to occur in rats [27] and dogs [11]. In the present study, nitrous oxide attenuated the action of convulsive doses of laudanosine and greater suppression may be expected, therefore, in the clinical situation in which the plasma concentrations of laudanosine are much smaller.

Although not statistically significant, there was a tendency for the anticonvulsant action of nitrous oxide to decrease with time. We have reported that acute tolerance develops to several CNS actions of nitrous oxide, such as slowing of EEG [12, 28], suppression of somatosensory evoked response [14], antagonism of enflurane [14] and amygdaloid kindling [15] convulsions, but not to the analgesic action [16]. When tolerance developed, the maximum effects of nitrous oxide occurred at 20–30 min, and then subsided gradually at 2–3 h. In the present study the action of nitrous oxide was examined both at a time of maximum effect and after prolonged exposure. The present data indicate that tolerance to the antagonistic effect of nitrous oxide was not significant statistically.

We conclude that nitrous oxide antagonizes the CNS stimulating action of laudanosine, and that the combined use of nitrous oxide and atracurium is an appropriate clinical procedure.

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EFFECTS OF SUXAMETHONIUM ON THE CEREBRUM FOLLOWING DISRUPTION OF THE BLOOD–BRAIN BARRIER IN DOGS

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SUMMARY

We have studied the effects of suxamethonium 1.0 mg kg^{-1} i.v. on cerebral blood flow (CBF), cerebral metabolic rate (CMRO_2), and the electroencephalogram (EEG) in dogs anaesthetized with halothane (1.0 MAC) following blood–brain barrier (BBB) disruption with intracarotid (i.c.) mannitol. The combination produced a transient increase in CBF, while CMRO_2 did not change. These responses were similar to those produced by i.c. mannitol plus i.v. saline. Suxamethonium produced desynchronization of the EEG that persisted longer than that produced by saline. In only one of the six animals was the desynchronization sustained (90 min) beyond that found in dogs with a normal BBB. We conclude that disruption of the BBB did not enhance the cerebral stimulating effects of i.v. suxamethonium, and did not increase the likelihood of seizure activity following suxamethonium.

KEY WORDS

Brain: blood–brain barrier, blood flow, electroencephalogram, metabolism, oxygen consumption. Neuromuscular relaxants: suxamethonium Complications: seizures.

Suxamethonium produces activation of the electroencephalogram (EEG) and increases in cerebral blood flow (CBF) in lightly anaesthetized subjects with an intact blood–brain barrier (BBB) [1]. The response is thought to be caused by a mechanism other than a direct effect on the brain [1, 2], as the drug does not cross the BBB [3]. In contrast, it produces EEG evidence of seizures when placed topically on the cerebral cortex [4]. This suggests that it may be capable of inducing cerebral stimulation or seizures in patients with impairment of the BBB. The present study tested this hypothesis by administering i.v. suxamethonium to dogs following osmotic disruption of the BBB.

MATERIALS AND METHODS

The programme for this study was approved by the Institutional Animal Care and Use Committee. Anaesthesia was induced and maintained with 1–3% halothane and nitrogen in oxygen in 12 unpremedicated mongrel dogs weighing 8.0–14.1 kg. The trachea was intubated without the aid of neuromuscular blockers and the lungs were ventilated with a Harvard ventilator. Ventilation and FI_{O_2} were adjusted to maintain Pa_{O_2} and Pa_{CO_2} close to 20.0 kPa and 5.3 kPa, respectively. Cannulae were inserted into a femoral artery for blood sampling and pressure measurements, and into femoral and forelimb veins for administration of fluids and drugs. Teflon cannulae (20-gauge, 32 mm) were inserted into the common carotid arteries bilaterally, with their tips at the junction of the external and internal carotid arteries, for the injection of mannitol. Heart rate (HR) was measured from a lead II electrocardiogram. During the preparatory period, dogs were given 0.9% saline solution

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20 ml kg^{-1} i.v. Sodium bicarbonate was given i.v. as needed to maintain a buffer base of approximately 40 mmol litre^{-1}.

After heparinization with 300–400 u kg^{-1} i.v., the sagittal sinus was exposed, isolated and cannulated as described previously [5]. This allowed blood sampling and provided direct measurement of CBF from the anterior, superior and lateral portions of both cerebral hemispheres, representing approximately 54% of the total brain weight [6]. Blood flow was recorded continuously using a square wave electromagnetic flow meter (ET 300 API, Carolina Medical Electronics) [7]. Blood oxygen contents were calculated from measurements of oxyhaemoglobin concentrations (CO-oximeter, IL 282) and oxygen tensions (IL electrodes) [8]. CMRo_2 was calculated as the product of CBF and the arterial–sagittal sinus blood oxygen content difference. A six-lead, three-channel bipolar (bifrontal, biparietal and bioccipital) EEG was recorded from electrodes glued to the calvarium. Brain temperature was monitored by a parietal extradural thermistor and maintained at 37 °C with heat lamps. Inspired and end-expired concentrations of halothane and carbon dioxide were measured with a mass spectrometer (Perkin-Elmer Model 1100). Serum osmolality was determined by the freezing point depression technique (Multi-Osmette, Precision Systems, Inc.). The ears of all dogs were plugged with cotton and their eyes were closed with tape.

Halothane concentrations were maintained at 0.87% end-expired (1.0 MAC) for 20 min before control measurements were taken. During the 20-min stabilization period, no additional i.v. fluids were given and ventilation and FI_{O_2} were unchanged. After control measurements were taken, dogs were assigned to one of two treatment groups: six dogs (group A) received intracarotid (i.c.) injections of mannitol, followed 3.0 min later by i.v. suxamethonium 1.0 mg kg^{-1} in 0.9% saline 3.0 ml; an additional six dogs (group B) received i.c. mannitol followed 3.0 min later by i.v. 0.9% saline 3.0 ml. The first dog in each of these groups received 25% mannitol 2.0 ml kg^{-1} into each carotid artery over 40 s (total dose 1.0 g kg^{-1}). This dose produced less than the desired amount of BBB disruption of the frontal cortex, so the remaining five dogs in each group received 25% mannitol 3.0 ml kg^{-1} into each carotid artery injected over 20 s (total 1.5 g kg^{-1}).

The combination of i.c. mannitol plus i.v. suxamethonium produced a mixed metabolic and respiratory acidosis and ventilation was increased by 30% concomitantly with administration of neuromuscular blocker in order to keep end-tidal carbon dioxide stable in those dogs. Following the 15-min measurement point in both groups of dogs, bicarbonate was given and ventilation was adjusted in an attempt to restore acid–base status to near control values.

Following the 15-min measurement point, all dogs were given i.v. infusions of 3% Evans blue dye 4 ml kg^{-1} over a 5-min period for determination of the integrity of the BBB [9]. Administration of this hypertonic solution, and the prior administration of mannitol i.c., produced a marked decrease in mean arterial pressure [10] which was countered with an infusion of phenylephrine 40 µg ml^{-1} in 0.9% saline solution during infusion of mannitol and Evans blue dye to maintain cerebral perfusion pressure > 50 mm Hg.

At the completion of the study, the dogs were killed with potassium chloride i.v. The brains were flushed with 0.9% saline solution through the carotid artery cannulae until the sagittal sinus effluent was clear. The brains were removed and weighed, rinsed with saline solution and stored in 3.7% buffered formalin solution. After a minimum of 4 weeks' storage, they were sliced in the coronal plane at five different sites between the frontal pole and the site of sagittal sinus cannulation. The degree of BBB disruption for each slice was scored according to a four-point scale [11]. The degree of BBB disruption for a given dog was defined as the median response of the various slices.

Following treatment with either suxamethonium or saline, data were grouped into 15-min measurement periods. For each measurement period, the mean response during the period was calculated as the integral of the response divided by time. Such an analysis reduced the number of comparisons within each group and between groups. The individual data points following either suxamethonium or saline treatment, in addition to data from the 15-min measurement intervals, were compared with the appropriate control data using a one-factor analysis of variance and F tests. Data from groups given suxamethonium were compared with those from groups receiving saline placebo, using Student's unpaired t tests. Data evaluating the degree of BBB staining were compared using the Mann–Whitney rank sum test. $P < 0.05$ was considered significant.

TABLE I. *Control variables (mean (SEM)) before blood–brain barrier disruption in dogs treated with either suxamethonium or placebo. CBF = Cerebral blood flow; CMRo$_2$ = cerebral metabolic rate; MAP = mean arterial pressure*

	Group A Suxamethonium 1.0 mg kg^{-1} i.v. ($n = 6$)	Group B Placebo i.v. ($n = 6$)
Weight (kg)	10.8 (0.7)	10.6 (0.7)
Pa_{O_2} (kPa)	20.1 (0.4)	20.1 (0.3)
Pa_{CO_2} (kPa)	5.2 (0.1)	5.1 (0.1)
pH	7.33 (0.01)	7.34 (0.02)
Buffer base (mmol litre^{-1})	41 (1)	41 (1)
Haemoglobin (g dl^{-1})	13.0 (0.7)	12.3 (0.8)
Serum osmolality (mosmol litre $^{-1}$)	295 (1)	296 (2)
CBF (ml 100 g^{-1} min^{-1})	67 (5)	70 (6)
CMRo$_2$ (ml 100 g^{-1} min^{-1})	3.64 (0.12)	3.88 (0.17)
MAP (mm Hg)	100 (3)	97 (4)
Brain temperature (°C)	37.1 (0.0)	37.1 (0.1)
Oesophageal temperature (°C)	37.2 (0.1)	37.1 (0.1)

RESULTS

Control systemic and cerebral variables measured immediately before BBB disruption are listed in table I. There were no significant differences between groups. Postmortem examination of the formalin-preserved brains demonstrated intraparenchymal Evans blue dye throughout the cortex, denoting BBB disruption. All slices in all dogs had some evidence of BBB disruption, and there was no significant difference between the amount of BBB disruption in the two experimental groups.

Mannitol i.c. produced EEG activation in all dogs; however, there was a difference between the EEG effect of mannitol plus suxamethonium (group A) and that of mannitol plus placebo (group B). In both groups, the control EEG consisted predominantly of an alpha rhythm with a superimposed delta rhythm. The alpha component was typically 8–10 Hz and 25–100 µV; the delta component was 2–4 Hz and 50–300 µV. In both groups, i.c. mannitol produced immediate desynchronization of the EEG. In one group B dog there was a 30-s period of mild desynchronization that was not typical of the degree or duration seen in the other 11 dogs. The activation in these 11 dogs was an increase in the frequency of the alpha rhythm to 12–14 Hz, with a reduction in the alpha amplitude of 30–50 %. There was also a concomitant elimination or attenuation of the delta component of > 80 %. In the five group B dogs showing EEG activation, the EEG returned to a synchronized pattern similar to that recorded in the control period (within 2–3 min in four, and within 4 min in one). The manner in which the EEG returned to a synchronized pattern in group B differed from that observed in group A: in the latter group, one dog had EEG desynchronization that persisted from the administration of mannitol to the 90-min measurement period. In an additional three dogs, the EEG remained desynchronized from the administration of mannitol until 3 min after suxamethonium. In the remaining two group A dogs, the mannitol-induced EEG changes returned to control values at 1.5 and 2.5 min after i.c. mannitol. Subsequent administration of suxamethonium produced a further period of desynchronization in both, similar to that observed following i.c. mannitol. The desynchronization persisted for 1.0 and 2.0 min, respectively.

EEG evidence of seizure activity was not observed in any animal. Neither mannitol plus suxamethonium in group A nor mannitol plus placebo in group B had an effect on CMRo$_2$. There were no differences in CMRo$_2$ between the two groups (fig. 1).

In group A, mannitol plus suxamethonium produced a significant increase in CBF from a control value of 67 (SEM 5) ml 100 g^{-1} min^{-1} to a peak value of 117 (9) ml 100 g^{-1} min^{-1} (a 75 % increase from control) at the 1-min measurement point. This was followed by a decline in CBF toward control values with time. This effect on CBF was similar to the effect of mannitol plus saline in group B (fig. 1). In group B, the control CBF was 70 (6) ml 100 g^{-1} min^{-1}. Injection of

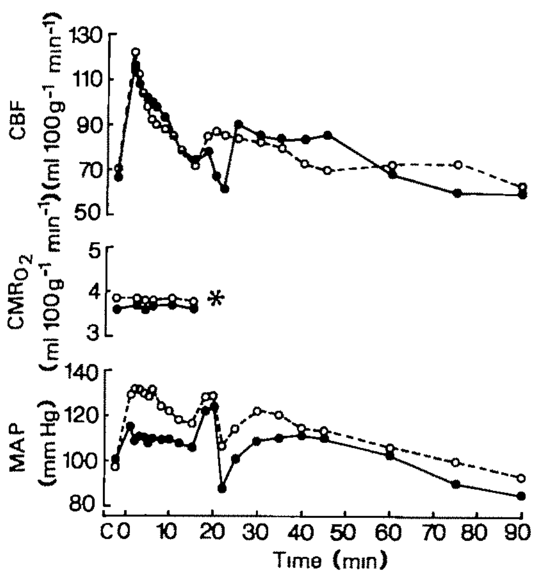

FIG. 1. CBF, CMRo$_2$ and MAP following suxamethonium (●) or placebo (○) treatment. Each point represents the mean response for six dogs. No significant differences between groups. C = Control period immediately before injection of mannitol. *Blood oxygen content, and thus CMRo$_2$, could not be measured spectrophotometrically after i.v. Evans blue dye.

mannitol plus i.v. saline produced a transient cerebral hyperaemia to a peak value of 122 (20) ml 100 g^{-1} min^{-1} (a 74 % increase from control) at the 1-min measurement period, and this was followed by a decline toward control values.

When the mean CBF during the 15-min intervals was compared with the control CBF, the 0–15 min CBF value increased significantly in group A. In this group, the mean 0–15 min value was 92 (8) ml 100 g^{-1} min^{-1} (a 37 % increase from control; $P = 0.02$ *vs* control). Although the CBF data over the same interval in group B did not achieve statistical significance at the $P < 0.05$ level, there was a tendency to increased flow. In group B, the mean 0–15 min CBF value was 90 (13) ml 100 g^{-1} min^{-1} (a 28 % increase from control; $P = 0.08$). When the mean CBF data from group A and group B were compared with each other, there were no significant differences at any measurement interval.

There was no significant change in MAP with time in group A. In contrast, in group B, there was an initial increase in MAP (probably related to an overzealous administration of phenylephrine) that was significantly different from control values at the 0–15 and 15–30 min measurement periods. However, there were no significant differences between groups at any measurement period, although there was a tendency to a greater MAP in group B at the 0–15 min period ($P = 0.08$).

There was a tendency for increases in Pa_{CO_2} after administration of mannitol and the study treatment in both groups A and B; however, in neither group did the values differ significantly from control, neither did the values differ between groups A and B.

DISCUSSION

When i.v. suxamethonium is administered to lightly anaesthetized subjects with normal BBB, the result is a brief period of EEG activation [1, 2] and increases in CBF [1, 2] and intracranial pressure [1, 12]. It is unlikely that the cerebral response is caused by direct interaction between the agent and cerebral neurones, because suxamethonium does not cross the BBB [3], and it has no effect on cerebral function when injected into the carotid arteries [13] or when given i.v. in subjects with spinal cord transection [13]. Instead of a direct neuronal effect, cerebral stimulation by suxamethonium has been attributed primarily to a modulation of cerebral function resulting from increased afferent input into the brain from muscle stretch receptors (increases in muscle afferent activity) [1, 2, 13].

Although i.v. suxamethonium can produce cerebral function alterations without crossing the BBB, there is some evidence to suggest that the direct contact between suxamethonium and cerebral neurones results in a more pronounced cerebral effect. Tan reported that topical application of suxamethonium to the brain resulted in EEG evidence of seizures [4]. Although suxamethonium has been administered to many patients with brain injury and disrupted BBB, the production of seizures by the drug in this context has never been recognized as a likely clinical phenomenon. However, this is confused by the fact that suxamethonium produces neuromuscular paralysis, thus the motor manifestations of any early seizure activity would be prevented, and suxamethonium is given usually with anaesthetic drugs, many of which are profound anticonvulsants (e.g. thiopentone). Finally, the presence of seizures in brain-injured subjects would probably be attributed to the brain injury, and not to a drug effect. The present study was designed to eliminate many of these confounding variables. Despite the study design, no convulsant effect of suxamethonium was demonstrated.

There are several factors that may explain the apparent discrepancy between the topical cortical effects and the absence of seizure activity when the myoneural blocker was given i.v. in the presence of disrupted BBB. First, direct application of suxamethonium to the cerebral cortex [4] results in neuronal concentrations in excess of those obtained following the i.v. administration of suxamethonium in the presence of disrupted BBB. Second, it is possible that our methods did not allow suxamethonium to pass the BBB. We did not measure the passage of suxamethonium across the BBB, but assumed that BBB disruption sufficient to allow the passage of Evans blue dye (charged; anhydrous molecular weight 961 Da before binding with proteins; molecular weight of dye–albumin complex approximately 68500 Da [9]) would also permit the passage of suxamethonium (charged; anhydrous molecular weight 361 Da; hydrated molecular weight 397 Da [14]). Thus direct passage of suxamethonium across the BBB was likely to have occurred.

In summary, the administration of clinically relevant doses of i.v. suxamethonium in the presence of osmotically disrupted BBB produced minimal alterations of cerebral function other than those attributed to BBB disruption alone. Specifically, no EEG, CBF or CMR_{O_2} evidence of intense cerebral stimulation or seizures was noted. We conclude that disruption of the BBB is not a contraindication to the use of i.v. suxamethonium.

ACKNOWLEDGEMENTS

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EFFECT OF HALOTHANE ON HYPOXIC AND HYPERCAPNIC VENTILATORY RESPONSES OF GOATS

S. O. KOH AND J. W. SEVERINGHAUS

SUMMARY

We have measured the ventilatory responses to increased inspired carbon dioxide and to hypoxia in four goats awake and at 0.5%, 1.0% and 1.25% end-tidal halothane concentration. While maintaining PE'_{CO_2} constant at each of three values (means 5.86, 6.45 and 7.2 kPa), PE'_{O_2} was reduced rapidly from more than 25 kPa to 5.3–6 kPa for 3 min to record the increase in ventilation. Eleven sets of these 24 steady state points were obtained (2 $PO_2 \times 3$ $PCO_2 \times 4$ anaes. = 24). The mean isocapnic hypoxic ventilatory response (HVR) was 6.52 (SD 2.58) litre min^{-1} (n = 33) when awake, 5.62 (3.48) litre min^{-1} at 0.5% end-tidal halothane (ns), 3.05 (2.02) litre min^{-1} at 1% and 2.91 (2.12) litre min^{-1} at 1.25%, the last two being reduced significantly from awake and 0.5% halothane ($P < 0.05$). With 1.25% halothane, HVR was reduced to 44.5 (18.6)% of the awake HVR. However, when HVR was expressed as % increase in ventilation produced by isocapnic hypoxia, it was 71 (19)% awake but 124 (65)% with 1.25% halothane, a significant increase *with halothane ($P < 0.05$). With 1.25% halothane, the carbon dioxide response slope decreased to 36.4 (26.4)% of control; hypoxia did not increase the slope significantly. Whereas previous studies in man have shown that halothane preferentially depresses hypoxic chemosensitivity and has a significant effect at 0.1 MAC, in the goat the hypoxic and carbon dioxide chemosensitivities were depressed equally. At 0.5% end-tidal concentration (about 0.5 MAC), halothane did not significantly depress hypoxic response.*

KEY WORDS

Anaesthetics, volatile: halothane. Ventilation: hypoxic ventilatory response, carbon dioxide response.

Halogenated hydrocarbon anaesthetic agents are known to decrease hypercapnic ventilatory response (HCVR) in a dose-dependent manner [1, 2]. They have been shown to depress more profoundly the hypoxic ventilatory response in man, even at low concentrations. Knill and Gelb obtained evidence that the hypoxic response was reduced to less than 30% of control at 0.1 MAC and was eliminated at 1.1 MAC, even at increased $P\text{CO}_2$ [3]. This confirmed that the depression of hypoxic response was more severe in man than had been reported in dogs [4, 5]. In decerebrate cats, Davies, Edwards and Lahiri showed that halothane depressed neural output responses of the carotid body to hypoxia and hypercapnia less than to nicotine and cyanide [6]. In rabbits and cats, Ponte and Sadler [7] reported that peripheral chemoreceptor response to severe hypoxia ($PE'_{O_2} \simeq 4$ kPa) was not depressed severely by anaesthetics.

MATERIALS AND METHODS

With institutional Review Committee approval, the following investigations were performed in four healthy young castrated male goats that had been prepared for studies of the effect of high altitude on the pH of the brain ECF over central chemoreceptors. Logistic and technical problems with carotid arterial loops and the electrodes had aborted that study. Carotid loops failed because of periarterial haemorrhage or clotting and the electrodes were too unstable for chronic studies. Each goat had a chronic tracheostomy. Therefore

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we made a comparison in these animals of the effects of halothane on chemosensitivity to hypoxia and carbon dioxide, as this could be accomplished by measuring end-tidal concentrations of halothane, oxygen and carbon dioxide. The object of the study was to test if goats showed the specific sensitivity of the hypoxic chemoreceptor response to even small residual amounts of halothane which has been reported previously only in humans [3].

The goats were studied in a stanchion, standing when awake and lying prone when asleep. For each study, a 7-French gauge cuffed vinyl tracheal tube was inserted after 4% lignocaine topical anaesthesia of the trachea. The goats breathed through a No. 2 Fleisch pneumotachograph connected to a non-rebreathing valve. Sufficient gas was delivered to a 4-litre anaesthesia inspired reservoir bag to keep it inflated.

Inspired minute ventilation was continuously recorded by electrically averaging the inspiratory flow with a 15-s time constant. Inspired and end-tidal $P\text{O}_2$ and $P\text{CO}_2$ were displayed continuously and recorded using a Perkin Elmer 1100 mass spectrometer sampling from the external end of the tracheal tube. End-tidal halothane concentration was measured using a Beckman LB2 infrared halothane analyser. Signals were recorded on chart recorders for later analysis. Pneumotachograph flow was calibrated over the range 0–60 litre min^{-1} with a precision flow meter precalibrated with a Tissot spirometer.

Inspired gas mixtures were prepared using flow meters for oxygen, air, nitrogen and carbon dioxide and a bypass halothane vaporizer through which the resulting gas mixture was passed. Responses were tested in awake goats and at end-tidal halothane concentrations of 1.25%, 1.0%

TABLE I. *Mean* (SD) *values* (n = *11*) *of ventilation in hyperoxia and isocapnic hypoxia* ($P\text{E}'_{O_2}$ = *5.3–6 kPa*) *at resting* $P\text{CO}_2$ *and at two values of increased* $P\text{CO}_2$, *awake and with 0.5%, 1.0% and 1.25% end-tidal concentrations of halothane in four goats.* †Not *significantly different from the awake value*; *all other means during anaesthesia differ significantly from awake* ($P < 0.05$). *HVR = Hypoxic ventilatory response at constant* $P\text{E}'_{CO_2}$; *Mean HVR = mean of the three* $P\text{CO}_2$ *values*; *HCVR = mean carbon dioxide response slopes combining two increased values of* $P\text{E}'_{CO_2}$. *ox = Hyperoxic*; *hypox = hypoxic*; $\dot{V}_I$ = *ventilation*; $\Delta\dot{V}_I = \dot{V}_I(hypox-ox)$; $F = \dot{V}hypox/\dot{V}ox$

	End-tidal halothane concn (%)			
	0 (Awake)	0.5	1.0	1.25
HVR				
$P\text{CO}_2$ = 0				
$P\text{E}'_{CO_2}$ (kPa)	5.86 (0.46)	7.50 (0.61)	8.26 (1.02)	9 56 (1.45)
$\dot{V}_{I,ox}$ (litre min^{-1})	5.80 (0.65)	3.92 (1.08)	2.72 (0.57)	1.55 (0.49)
$\dot{V}_{I,hypox}$ (litre min^{-1})	11.64 (2.78)	7.78 (3.61)	5.09 (1.64)	4.84 (2.85)
$\Delta\dot{V}_I$ (litre min^{-1})	5.84 (2.71)	3.86 (3.20)†	2.37 (1.46)	3.29 (2.67)
F	2.01 (0.48)	1.98 (0.75)†	1.90 (0.59)†	3.11 (1.47)
$P\text{CO}_2$ step 1				
$P\text{E}'_{CO_2}$ (kPa)	6.45 (0.44)	8.51 (0.66)	9.49 (0.97)	10.72 (1.38)
$\dot{V}_{I,ox}$ (litre min^{-1})	10.18 (2.31)	7.75 (1.91)	4.64 (0.66)	5.29 (3.76)
$\dot{V}_{I,hypox}$ (litre min^{-1})	17.69 (3.43)	15.55 (4.82)†	8.17 (2.51)	8.25 (3.16)
$\Delta\dot{V}_I$ (litre min^{-1})	7 51 (2.24)	7.80 (3.91)†	3.54 (2.33)	2 95 (1.77)
F	1.76 (0.26)	2.02 (0.48)†	1.77 (0.55)†	2.07 (1.03)†
$P\text{CO}_2$ step 2				
$P\text{E}'_{CO_2}$ (kPa)	7.20 (0.48)	9.44 (0.50)	10.44 (1.06)	11.96 (1.35)
$\dot{V}_{I,ox}$ (litre min^{-1})	18.06 (2.83)	14.52 (3.09)	7.47 (2.13)	7.52 (3.46)
$\dot{V}_{I,hypox}$ (litre min^{-1})	24.25 (1.30)	19.71 (4.53)	10.72 (2.69)	10.00 (2.45)
$\Delta\dot{V}_I$ (litre min^{-1})	6.20 (2.70)	5.19 (2.13)†	3.25 (2.16)	2.48 (1.93)
F	1.35 (0.15)	1.36 (0.14)†	1.48 (0.38)†	1.53 (0.59)†
Mean HVR				
$\Delta\dot{V}_I$ (litre min^{-1})	6.52 (2.58)	5.62 (3.48)†	3.05 (2.02)	2.91 (2.12)
% of awake value	100	84.7 (31.1)†	45.5 (23.9)	44.5 (18.6)
F	1.71 (0.19)	1.79 (0.40)†	1.71 (0.43)†	2.24 (0.65)
HCVR (litre min^{-1} kPa^{-1})				
Hyperoxic	9.19 (3.42)	5.00 (1.71)	2.07 (0.83)	2.93 (2.03)
% of awake value	100	56.9 (18.0)	24.2 (9.1)	36.4 (26.4)
Hypoxic	9.98 (3.39)	6.78 (2.26)	2.66 (1.47)	2.41 (1.11)

and 0.5 % (in that order) because lighter levels of anaesthesia could not be studied first as a result of excitement. Deeper levels were not tested because, in preliminary tests, apnoea occurred at 1.5 %. At each level of anaesthesia the first measurements were made after 30 min of equilibration in order to attain relatively stable brain concentrations of halothane [8]. At each anaesthetic level, two values of increased end-tidal $P\text{CO}_2$ were obtained (mean values of 0.6 and 1.3 kPa greater than control), allowing 7–10 min for stabilization at each value. The hypoxic response was tested at each $P\text{CO}_2$ by changing the gas mixture delivered to the halothane bypass type vaporizer from an air–oxygen to an air–nitrogen mixture adjusted to reduce end-tidal oxygen tension rapidly to 5.7–6.4 kPa and holding it constant for at least 2 min while maintaining $P\text{E}'_{\text{CO}_2}$ constant at its hyperoxic value. The carbon dioxide slope was computed by linear regression. Hypoxic ventilatory response (HVR) was computed in two ways: $\Delta\dot{V}\text{I}$, the isocapnic increase in ventilation (litre min^{-1}); F, the hypoxic ventilatory ratio ($\dot{V}\text{hypox}/\dot{V}\text{ox}$).

Analysis of variance was used to assess differences, using Dunnett's test for multiple value differences from a single control, with $P <$ 0.05 taken as significant.

RESULTS

The means of 11 sets of data collected in the four goats (two to four in each animal over the course of 6 weeks) is shown in table I. Mean ventilation is plotted in figure 1 as a function of $P\text{E}'_{\text{CO}_2}$ at the four levels of anaesthesia during hyperoxia and hypoxia. At equal concentrations of halothane, the depression of HVR was not significantly different from that of HCVR, both decreasing by about 60 % at 1.25 % halothane (fig. 2). HVR at 0.5 % end-tidal halothane was not different from

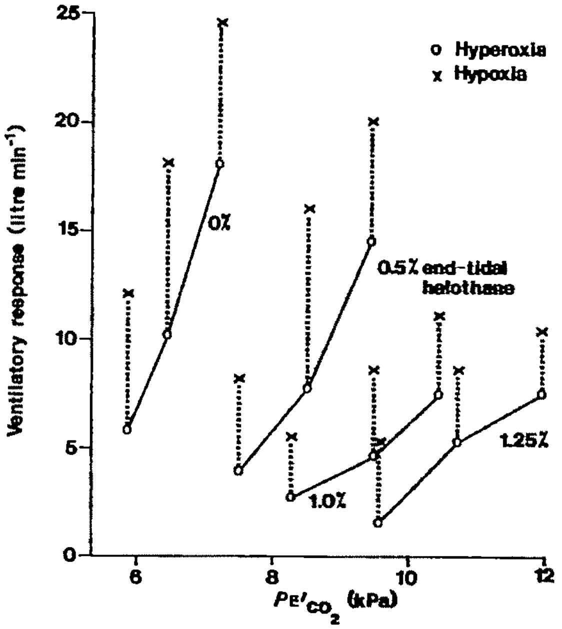

FIG. 1. Ventilatory responses to carbon dioxide and to hypoxia at each carbon dioxide concentration awake and at three end-tidal halothane concentrations in four goats (11 complete data sets).

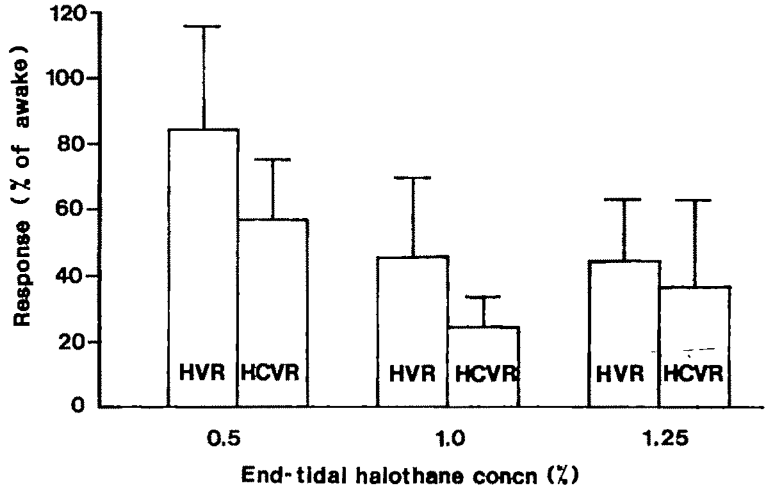

FIG. 2. Mean (SD) depression by halothane from awake responses of isocapnic hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR) in four goats. $n = 11$.

the awake response. The ventilatory ratio F increased with deep halothane anaesthesia. Isocapnic hypoxia increased ventilation by 71 (19)% awake and 124 (65)% with 1.25% halothane ($P < 0.05$). Hypoxia had no significant effect on the slope of the carbon dioxide response either awake or at any concentration of halothane tested.

DISCUSSION

The effects of halothane anaesthesia on respiratory control has not been studied previously in the goat, and our data may not reflect changes in other species. The absence of arterial blood samples weakens our conclusions, as end-tidal gas tensions may not reflect arterial values, especially with shallow breathing in deep anaesthesia [9]. Ideally, we should have determined Sa_{O_2} directly. Pulse oximeters were tried also, but functioned only intermittently on the ear or over the carotid loop. (In subsequent studies, the Ohmeda pulse oximeter ear probe was found to function commonly, but not uniformly, on the goat ear and to correlate remarkably well when functioning with arterial oxygen saturation down to 30%.)

Insertion of a cuffed tube into the trachea of an awake goat may have stimulated awake ventilation and our data interpreted subsequently as ventilatory depression with anaesthesia. However, the animals usually coughed for a few seconds after intubation of the trachea under topical anaesthesia, but showed no subsequent evidence of discomfort or tachypnoea. The anaesthetic depressant effect on ventilatory response to carbon dioxide is in accord with previous studies [1, 2] but, in contrast with studies in man [3], hypoxic response was not more depressed than carbon dioxide response and the hypoxic ventilatory ratio F was *increased* at 1.25% halothane ($P < 0.05$).

In other species, hypoxic drive mediated through carotid chemoreceptors is highly dependent on $P\text{CO}_2$, and therefore is considered generally to operate by enhancing carbon dioxide drive. Thus when carbon dioxide drive is depressed by halothane, although total ventilation is less, one might attempt to compute the partial separate effect of hypoxia as a fractional change in ventilation or in carbon dioxide slope. In the goat, hypoxia increased ventilation proportionally more in deep halothane anaesthesia than in awake animals, but did not interact with carbon dioxide as in other species. Surprisingly, the hypoxic response was not increased significantly by hypercapnia at any concentration of halothane even though, via the Haldane effect, hypercapnia must have reduced arterial saturation at constant alveolar $P\text{O}_2$. It is possible that greater ventilation induced by increasing $P\text{CO}_2$ may have reduced the difference between end-tidal and arterial $P\text{O}_2$.

The effect of halothane on $P\text{CO}_2$ appears to vary widely between species, implying differences of central and peripheral chemoreceptor sensitivity [10]. Peripheral chemoreceptor hypoxic sensitivity is depressed by chronic hypoxic exposure [11]. The effect of halothane on resting $P\text{CO}_2$ may be less than its effect on the carbon dioxide response slope [2, 3]. In the study of Knill and Gelb, at 1.1 MAC halothane in man ventilatory response to carbon dioxide was decreased to 36% of the awake response, while $P\text{CO}_2$ was unchanged from its awake value of 5.7 kPa [3]. In dogs at 1 MAC halothane, ventilation and resting $P\text{CO}_2$ did not change significantly [4].

Minute ventilation during isocapnic hypoxia increases linearly with arterial desaturation [12]. In our study, Sa_{O_2} was not measured, but at constant $P\text{E}'_{O_2}$, Sa_{O_2} should have decreased as $P\text{E}'_{CO_2}$ increased, reducing pH_a. Thus, as halothane MAC increased, a lesser Sa_{O_2} (at constant $P\text{E}'_{O_2}$) may have sustained ventilation in these goats, and contributed to the apparently well preserved hypoxic response.

Hypoxia did not increase the carbon dioxide response slope either awake or under halothane anaesthesia. Interaction in the ventilatory response between hypoxia and carbon dioxide has been shown to originate primarily in the arterial chemoreceptors [13, 14]. The mechanisms of carotid and aortic body stimulation are different for carbon dioxide and oxygen [15, 16]. Ponte and Sadler [7], recording carotid chemoreceptor nerve action potentials in rabbits and cats, showed persistently brisk responses to severe hypoxia ($\simeq$ 4 kPa) in the presence of several volatile anaesthetics—an effect not seen at greater values of $P\text{O}_2$ in previous studies [6]. They suggested that, in severe hypoxia, peripheral chemoreceptor drive to the respiratory centres remains undepressed by anaesthetics, although response at more moderate values of hypoxia was attenuated, by a shift of the response curve to decreased $P\text{O}_2$. Their study and the present data suggest an alternate hypothesis for the mechanism of the observed differences between goat and man, namely a species difference in the effect of halothane on the oxygen threshold of peripheral chemoreceptor response. To test if the response threshold is offset to decrease Po_2 and Sa_{O_2} in man would require use of an unacceptably low oxygen saturation.

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SINUS ARREST INDUCED BY TRIVIAL NASAL STIMULATION DURING ALFENTANIL–NITROUS OXIDE ANAESTHESIA

P. L. BAILEY

SUMMARY

A case is reported of bradycardia and sinus arrest induced by insertion of a nasal temperature probe. Other possible causes of bradycardia and sinus arrest under anaesthesia are reviewed briefly. Evidence for the neurological basis of a nasocardiac reflex, similar to the oculocardiac reflex, is presented. A minor, trivial stimulus may elicit this reflex.

KEY WORDS
Complications: arrhythmia. Surgery: gynaecological.

Several reports have described severe bradycardia and sinus arrest or asystole during opioid-based anaesthesia [1–7]. Although opioids are known to enhance vagal tone and promote, induce or cause bradycardia, in all reports of serious arrhythmias other drugs (β-adrenergic blockers, calcium entry blockers, neuromuscular blockers) have also been implicated. In addition, laryngoscopy and tracheal intubation may produce bradycardia, although sympathetic stimulation may also result. This report documents severe bradycardia and sinus arrest induced by trivial nasal stimulation in an otherwise healthy adult during alfentanil–nitrous oxide in oxygen anaesthesia.

CASE REPORT

A 19-yr-old, 1.65-m, 65-kg female was scheduled for dilatation of the cervix and curettage of the uterus for retained placenta. She had undergone uneventful vaginal delivery 2 days previously. She was afebrile and had a heart rate of 88 beat min^{-1} and an arterial pressure of 95/55 mm Hg. She was otherwise healthy, but had a history of cigarette smoking. PCV was 30%. She did not appear anxious and was given no premedication. An 18-gauge i.v. cannula was inserted and, in the operating room, monitoring with a three-lead electrocardiograph, automatic arterial pressure cuff, precordial stethoscope and pulse oximeter was begun. The patient's lungs were preoxygenated with 100% oxygen using a circle system and face mask and she subsequently received vecuronium 1 mg and droperidol 0.625 mg i.v. Two minutes later the patient was given alfentanil 50 μg kg^{-1} as an i.v. bolus over 15 s, followed by thiopentone 225 mg and suxamethonium 100 mg. Laryngoscopy and intubation were performed with a No. 3 Macintosh blade and a tracheal tube (7.5-mm i.d.) without difficulty. Breath sounds were present bilaterally and equal. Heart rate was 57 beat min^{-1} (fig. 1: upper ECG trace) and arterial pressure 90/60 mm Hg after intubation. A nitrous oxide–oxygen mixture (2:1) was administered via a circle system for maintenance of anaesthesia in combination with an infusion of alfentanil 1 μg kg^{-1} min^{-1}. Ventilation was controlled mechanically with a tidal volume of 700 ml and ventilatory frequency 8 b.p.m.

A temperature probe (Yellow Springs) protected by an American Safe Temp sleeve, was inserted approximately 2.0 cm in the left nares; this caused a sudden and profound decrease in heart rate to 33 beat min^{-1} (fig. 1: second ECG trace). Heart rate returned to 60 beat min^{-1} upon withdrawal of the temperature probe. Haemodynamically, the patient was otherwise stable (arterial pressure 94/60 mm Hg). The operation had not yet begun, and no signs of inadequate anaesthesia (tears or movement) were present.

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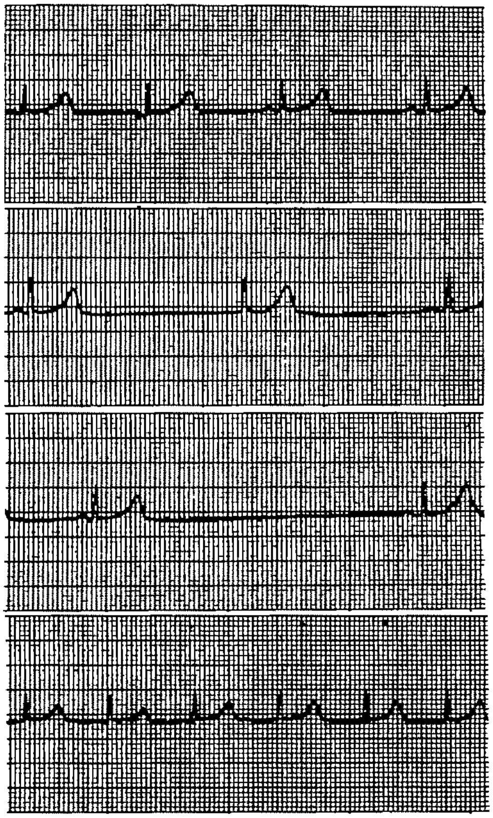

FIG. 1. Electrocardiographic changes associated with alfentanil–nitrous oxide–oxygen anaesthesia and insertion of a nasal temperature probe. Upper trace; ECG after induction of anaesthesia and before arrhythmias. Second trace: bradycardia induced by insertion of nasal temperature probe. Third trace: near sinus arrest induced by insertion of nasal temperature probe. Fourth trace: rapid junctional rhythm produced by atropine 0 4 mg i.v.

Train-of-four stimulation with a peripheral nerve stimulator produced four twitches. Insertion of the temperature probe in a similar manner was repeated six times in order to verify causality and record the events on the electrocardiogram. Each time a significant bradycardia or sinus arrest of almost 3 s duration (fig. 1: third ECG trace) immediately ensued. Removal of the probe always led to a resolution of the arrhythmia. Atropine 0.4 mg i.v. was administered, causing a rapid junctional rhythm of 90 beat min^{-1} (fig.1: fourth ECG trace). Insertion of the temperature probe after atropine produced no further change in the electrocardiagram. The operation proceeded uneventfully and normal sinus rhythm returned during operation. The infusion of alfentanil was discontinued 15 min before surgery ended. Total surgical time was 30 min. Residual neuromuscular block was antagonized with edrophonium 60 mg and atropine 0.6 mg i.v. at the conclusion of the operation. Nitrous oxide was discontinued, spontaneous ventilation resumed and the trachea was extubated. The patient had an uneventful postoperative course.

DISCUSSION

Rivard and Lebowitz [6] have reported bradycardia and asystole after induction of anaesthesia with alfentanil and suxamethonium. Laryngoscopy, tracheal intubation and ventilation with 100% oxygen restored sinus rhythm without other pharmacological therapy [6]. Maryniak and Bishop [2] also reported two cases of sinus arrest associated with induction of anaesthesia with alfentanil and suxamethonium that occurred when the larynx was sprayed with lignocaine [2]. In both patients, sinus rhythms returned spontaneously. Explanations for the occurrence of these rhythm disturbances include vagomimetic effects of opioids, especially potent and rapid acting agents such as alfentanil [8]; enhanced vagal tone induced by suxamethonium, because of breakdown products, ganglionic stimulation, or both; and stimulation of vagally innervated structures such as the larynx.

The significant bradycardia and brief sinus arrest sustained by our patient differed from those mentioned above. The arrhythmias occurred in our patient approximately 10–15 min after the initial injection of alfentanil 50 µg kg^{-1}. Maryniak and Bishop [2], and others [9], suggest that peak plasma concentrations of alfentanil and peak effect would have occurred sooner. Thus alfentanil probably did not cause the arrhythmias in our patient. Similarly, suxamethonium was not related temporally as a direct cause. Other possible mechanisms, for example surgical stimulus, were not present, as surgery had not yet begun. In addition, our patient had a stable haemodynamic state until the insertion of the nasal temperature probe which repeatedly and consistently caused the problem described.

Sensory innervation of the nasal mucosa is provided by the maxillary and ophthalmic divisions of the trigeminal nerve, which have their cell bodies located in the Gasserian ganglion. The anterior portion of the nose, the part most likely to have been stimulated in our patient, is innervated by the anterior ethmoid nerve, which arises from the nasociliary branch of the ophthalmic division of the trigeminal nerve. Sympathetic and parasympathetic nerve fibres also accompany the anterior ethmoid nerve [10]. Interestingly, the ophthalmic division of the trigeminal nerve and Gasserian ganglion are involved also in the oculocardiac reflex. Bradycardias and other arrhythmias are well known to occur during eye surgery. Atropine-induced arrhythmias have been observed also during treatment of oculocardiac reflex related bradycardias [11]. Atropine also induced a junctional rhythm in our patient. In atropine moderate doses, may inhibit vagal influence on the atrio–ventricular node before affecting the sinus node, allowing for junctional escape rhythms [12]. Thus it appears that there exists a nasocardiac reflex similar to the oculocardiac reflex.

A search of the literature reveals reports describing various nasocardiac reflexes with a neurological basis in the trigeminovagal arc [10, 13–16]. These reports document that stimulation of the nasal mucosa may elicit a host of responses including apnoea, closure of the larynx, bradycardia, arrhythmias, vasomotor changes and sudden death [10, 13]. Death after trivial nasal stimulation, for example sneezing, has been reported in patients with myocardial disease [14, 15]. Baxandall and Thorn [16] have reported profound bradycardia in an anaesthetized patient during turbinate bone manipulation. These authors describe the maxillary division of the trigeminal nerve (the innervation of the turbinates) as the afferent limb of this nasocardiac reflex. In our patient, the anterior part of the nose was stimulated, implicating the anterior ethmoidal nerve and ophthalmic division of the trigeminal nerve as the afferent limb of the nasocardiac reflex [17]. In addition, our report is highlighted by the trivial nature of the stimulus producing bradycardia and sinus arrest.

In conclusion, we have observed that an apparently minor stimulus, the insertion of a nasal temperature probe, may induce significant bradyarrhythmias and sinus arrest. The role that anaesthesia with alfentanil and suxamethonium played in our patient is unknown. A neurological basis for a nasocardiac reflex exists and may be similar to the oculocardiac reflex in terms of mechanism and treatment.

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7TH NERVE PALSY AFTER EXTRADURAL BLOOD PATCH

D. M. LOWE AND A. M. McCULLOUGH

SUMMARY

We describe a patient who developed a 7th cranial nerve palsy following an extradural blood patch; full recovery followed. The likely aetiology is discussed.

KEY WORDS

Anaesthetic techniques extradural Complications: VII n. palsy.

CASE REPORT

A 24-yr-old patient in her second pregnancy was admitted in early labour at term with a history of reduced fetal movements during that day. On examination labour was confirmed and cardiotochographic monitoring was initiated. An infusion of syntocinon was started and an extradural requested for analgesia. An anaesthetic registrar inserted, on the second attempt, an extradural catheter via the L2–3 interspace with the patient in the left lateral position. The patient complained immediately of headache; this was frontal and severe. Dural puncture was not suspected. Extradural analgesia was established with a total of 0.5% plain bupivacaine 7 ml. No CSF was aspirated through the needle or catheter. The headache subsided initially and no specific treatment was offered. The extradural was topped up once with 0.5% plain bupivacaine 8 ml (2-ml test dose + 6 ml) and the patient had a normal vaginal delivery. There was no evidence of unduly extensive block.

On transfer to the postnatal ward, the patient still complained of mild headache, but was able to walk after the extradural had worn off. By 18 h after insertion of the extradural catheter, the headache had become severe and she felt too unwell to get out of bed. At this time, the headache was frontal, made worse by sitting and improved on lying down. On questioning, the patient said the nature of the headache had not changed since the extradural catheter had been inserted, but the severity had increased. A low CSF pressure headache was diagnosed.

Despite conservative treatment with bed rest, oral analgesics and copious fluids, the patient's condition did not improve, and so on the 4th day after delivery she was offered an extradural blood patch. This was performed via the L2–3 interspace with 20 ml of autologous blood under aseptic conditions, with an immediate cure of her headache. During the extradural injection of blood, she did not complain of back pain, paraesthesia or any other sign of neural compression.

Eight hours later, the patient complained of a left-sided facial weakness which had appeared gradually over the previous 4 h. On examination, she had a lopsided smile and, on testing, the muscles of the left side of the face and forehead were weaker. There was no sensory deficit. A partial 7th cranial nerve lower motor neurone lesion was diagnosed. Hearing, taste and the other cranial nerve functions were normal. No treatment was given. There was no evidence of herpes reactivation (she had regular episodes of oral herpes).

Over the next 2 days the signs and symptoms persisted unchanged. She was allowed home. But, 3 weeks after discharge, she was referred urgently to a physician with back pain and presumed root irritation, but failed to keep her appointment. At follow up 7 weeks after delivery, she had made a complete recovery and said that normal 7th nerve function had returned 4 weeks after the blood patch. Her back problem had resolved spontaneously and no physical signs were found.

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DISCUSSION

Accidental dural puncture following extradural analgesia is a relatively common complication [1]. If untreated, this resolves normally within 1 week, but may last much longer [2]. Following childbirth, an incapacitating headache prevents a mother from looking after her baby and spoils an otherwise pleasant experience. If simple measures are not effective, a blood patch should be offered [3].

Cranial nerve palsies following dural puncture are well described and are usually explained on the basis of CSF loss causing descent of the brain and stretching of the nerve [4]. Effects on the 3rd, 4th, 6th, 7th and 8th nerves have been described. Abouleish and colleagues reported one case of facial paralysis following blood patch in 185 patients, but noted that it occurred 4 days afterwards and dismissed it as coincidence [5]. Computerized literature search (Medline) produced no other reports.

The incidence of idiopathic facial paralysis (Bell's palsy) is 27 per 100000 per annum [6] and this increases by a factor of three in pregnancy [7]. The sudden onset of paralysis within 4 h of a blood patch, with no subsequent progression, suggests a relationship between the two events. The lack of effect on taste (chordae tympanae) locates the lesion within the facial canal [8].

In Bell's palsy, the 7th nerve is acutely swollen within the facial canal. Loss of function is presumed to be a result of relative ischaemia and treatment, if any, is aimed at relieving compression of the nerve which, at this point, is an intracranial structure.

Within the cranium, mean perfusion pressure equals mean arterial pressure minus central venous pressure and intracranial pressure (ICP). We suggest that the sudden increase in ICP caused by the blood patch which cured the headache may have compromised the blood supply to this part of the 7th nerve. It is possible that our patient already had a swollen nerve and was liable to develop a palsy, but it was precipitated by the blood patch.

7th nerve palsy has not previously been ascribed to extradural blood patching. We suggest that in this patient the palsy was secondary to the extradural blood patch. If the paralysis is incomplete, complete recovery may be anticipated [6].

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ANAESTHETIC HAZARDS OF AORTOCAVAL FISTULA

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SUMMARY

A 66-yr-old man was anaesthetized for repair of a suspected ruptured aortic aneurysm. He became deeply cyanosed and suffered two episodes of asystole as the surgeons entered the abdomen. After the aorta was cross-clamped his condition improved markedly and no further problems ensued. Surgical exploration demonstrated intact aneurysms of the aorta and left iliac artery, the former containing a 3–4 cm long aortocaval fistula. The aneurysms and fistula were repaired and his further course was uncomplicated. Potential causes for the cyanosis and cardiac arrest in this patient are discussed.

KEY WORDS

Complications: aortocaval fistula Surgery: aortic aneurysm.

CASE REPORT

A 66-yr-old man presented via the accident department with a history of 4 days abdominal and lower back pain. He had developed oliguria over 24 h. His past medical history included exertional angina and a myocardial infarct 10 years previously. He was taking a thiazide diuretic for mild hypertension. On examination he was sweaty, pale and in obvious discomfort from a painful pulsatile abdominal swelling. His heart rate was 110 beat min^{-1} and arterial pressure 160/90 mm Hg; there were no signs of congestive heart failure. His lower limbs were mottled and swollen but retained palpable peripheral pulses, whilst the superficial veins of the lower limbs and abdomen were not obviously distended. There was no venous congestion of the head and neck. ECG demonstrated no signs of acute myocardial ischaemia. A diagnosis of ruptured aortic aneurysm was made.

Two large-gauge peripheral cannulae and a right subclavian central venous catheter were inserted and he was brought to the operating theatre without premedication. One litre of 0.9% saline was infused before surgery. The central venous pressure was +8 cm H_2O before induction of anaesthesia (the catheter was seen to lie in the right internal jugular vein on a later chest x-ray). The haemoglobin concentration was 14 g dl^{-1} before operation.

In the operating theatre, a urinary and left radial artery catheter were inserted using local anaesthesia. The abdomen was prepared and draped for surgery. Anaesthetic monitoring included continuous ECG, measurement of direct and indirect arterial pressure, end-tidal carbon dioxide, fractional inspired oxygen and anaesthetic vapour concentrations. After preoxygenation, a rapid sequence induction was performed with the administration of etomidate 10 mg and suxamethonium 75 mg. The trachea was intubated and anaesthesia maintained with fentanyl 300 μg, atracurium 25 mg and 60% nitrous oxide and 1% enflurane in oxygen. The heart rate and arterial pressure remained stable during the period of intubation.

Surgery was commenced immediately after induction and tracheal intubation. On entering the abdomen, all bleeding points were noted to be deeply cyanosed. The intestine was discoloured, with gross venous engorgement. Simultaneously, the patient's head and neck became increasingly plethoric and cyanosed. The question of oesophageal intubation or other causes of hypoxia were considered. Manual inflation of the lungs was performed with 100% oxygen and the position of the tracheal tube rechecked by direct laryngoscopy and hearing bilateral air entry in the chest. Progressive sinus bradycardia, hypotension and asystole rapidly followed. I.v. calcium chloride 10 mmol and adrenaline 1 mg were given while external cardiac massage was performed by

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the surgical team. A sinus bradycardia (40 beat min^{-1}) with hypotension (AP 50/30 mm Hg) returned within 2 min to be followed rapidly by another episode of bradycardia and asystole. A further 0.25-mg bolus of adrenaline was given. Whole blood 1000 ml was infused rapidly during this period.

The aorta was cross-clamped as quickly as possible, after which cardiac output rapidly returned. The iliac arteries were clamped also. Incision of the intact aneurysm sac revealed a 3-cm long aortocaval fistula with approximately 400 ml of loose clotted blood within the aneurysm. Brisk venous bleeding through the fistula was controlled by digital pressure initially and then by passing balloon catheters above and below the fistula via the femoral vein. After the aorta had been cross-clamped the patient developed hypertension (AP 250/110 mm Hg) and tachycardia (190 beat min^{-1}). These disturbances settled over 10–15 min, when the inspired concentration of enflurane was increased and practolol 5 mg and fentanyl 200 μg were administered. The aneurysms were repaired using a dacron aorto–bifemoral graft and the vein repaired by direct suture.

The remainder of the anaesthetic was uncomplicated. No further significant inotropic support was required, a good diuresis (1550 ml) followed the administration of 20% mannitol 100 ml and an infusion of dopamine 2 μg kg^{-1} min^{-1}. A total of 10 units of blood and 4 units of fresh frozen plasma were given, mainly to cover heavy blood loss from a bleeding iliac vein, damaged by a balloon catheter. The patient was returned to the intensive care unit overnight, where recovery was uneventful. Minor disturbances of coagulation were observed over the next 2 days, but no further blood products were needed. There were no significant disturbances of cardiovascular, respiratory, hepatic or renal function in this period. The patient left hospital 9 days after surgery with some residual swelling of both legs.

DISCUSSION

Aortocaval fistula is an uncommon but well recognized complication of aortic aneurysm which may present both acutely and chronically [1–3]. The incidence has been estimated as 1–4% [3] of aortic aneurysms, but it was not mentioned in a literature search related to anaesthesia, or in recent reviews on anaesthesia for aortic aneurysm surgery [4, 5]. Less commonly, the aetiology may be traumatic, following accidents or lumbar disc surgery. Rare causes include syphilis, mycotic aneurysms, Marfans syndrome and Ehlos–Danlos syndrome [1]. The complications of arteriovenous fistulae relate to their size, anatomical location and the cardiac reserve of the patient. Common late presentations include high output cardiac failure, abdominal pain, limb discolouration and oedema. Traumatic fistulae may be entirely asymptomatic or present insidiously, as they tend to be smaller and occur in younger patients who have otherwise normal vasculature and a greater cardiac reserve.

Acute decompensation, as occurred in this patient, is reported less often and usually involves rupture of an associated aneurysm sac. Many such patients would not survive to reach hospital. In this patient, as in other reports [2], the fistula was not recognized before operation. The presence of discoloured swollen lower limbs should have raised suspicion that a fistula might be present in this patient, and other signs, including a bruit, high central venous pressure or cardiovascular decompensation, were not recognized. Increases in venous pressure may be limited to the lower limbs and may not cause an increase in central venous pressure [3]. A bruit may be intermittent or absent as thrombus blocks the fistula.

It is postulated that the acute deterioration in this patient followed surgical disturbance of blood clot which was partially blocking the fistula. The large fistula then allowed a significant part of the cardiac output to flow into the inferior vena cava. This low resistance pathway would minimize arterial pressure and flow to vital areas such as the coronary circulation, causing rapid haemodynamic collapse. The rapid development of cyanosis would follow from a combination of venous hypertension and low arterial flow. Such a sudden haemodynamic collapse would be accentuated in the presence of ischaemic heart disease, as present in this patient. Alternatively, the induction of anaesthesia may have precipitated haemodynamic decompensation if the unrecognized fistula was already patent.

The choice of anaesthetic agents used in this patient was designed to maintain cardiac stability. The sequence of anaesthetic induction with etomidate, suxamethonium, positive pressure ventilation, nitrous oxide and enflurane would be expected to cause a reduction in cardiac output and arterial pressure. Progressive bradycardia and asystole would not be expected in the absence of severe blood volume depletion or cardiac dysfunction. Major blood loss was not a problem at induction of anaesthesia as the aneurysm sacs were intact and there was only about 400 ml of clotted blood in the sacs. When surgical control of the aneurysm was achieved, there was no further haemodynamic deterioration. Reperfusion and significant blood loss produced no further haemodynamic deterioration. There was no evidence of perioperative myocardial ischaemia on serial electrocardiograms and cardiac enzyme studies. Unfortunately, the central venous pressure was not measured during the cardiac arrest, as the intraoperative measurements were performed intermittently by U-tube manometer. When stability was returning, CVP was +10–12 cm H_2O. An adverse reaction to anaesthetic drugs was considered unlikely in the absence of bronchospasm, cutaneous vasodilatation and rapid improvement after aortic cross-clamping.

Embolization of blood clot, atheromatous debris or air through the fistula has been reported to be a cause of cardiovascular collapse in such patients [3]. This cause was not considered at the time, but is unlikely as collapse occurred before the aneurysm was opened. Early surgical control of arterial and venous limbs of the fistula is essential to avoid this complication.

Surgical closure of arteriovenous fistulae has been associated with a bradycardia termed the Nicoladoni (Branham) sign. This reflex may be elicited also by digital pressure on a peripherally sited arteriovenous fistula. The proposed mechanism for this reflex involves arterial baroreceptors sensing increases in systemic arterial pressure as the fistula is closed; reflex bradycardia follows, mediated by the vagus [6]. In the circumstances of this case, no such reflex was seen.

The optimum anaesthetic management of the patient with a significant arteriovenous fistula has not been reported. In the presence of a significant fistula, arterial pressure is maintained by increased cardiac output and drugs or manoeuvres should be chosen to minimize such changes. Drugs causing vasodilatation may reduce flow through a fistula, but their effects would be unpredictable and likely to worsen systemic haemodynamics. Vasopressor drugs may be ineffectual because of increased shunting of blood through the fistula. Early surgical control of the fistula is the key to achieving haemodynamic stability, as demonstrated in this patient. As in the case of a ruptured aneurysm, anaesthesia should not be induced without the abdomen prepared, with surgeons scrubbed and ready to enter the abdomen. Anaesthetists should be vigilant for the presence of related or separate cardiovascular pathology in such patients, which may be missed in the haste to get to theatre. The optimum anaesthetic technique is probably a high-dose opioid and neuromuscular blocker technique, as this minimizes changes in cardiac output and systemic vascular resistance.

Control of a fistula can be achieved rapidly after laparotomy by conventional cross-clamping above and below the fistula. Alternatively, control can be achieved by passing balloon catheters above and below the fistula, if necessary under x-ray control. Venous control above and below the fistula is necessary to control bleeding into the open aneurysm sac and potential embolization. If problems are anticipated before surgery, balloon catheters may be passed via the femoral vessels under local anaesthesia, before induction of general anaesthesia.

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I.V. FLUIDS DURING SURGERY

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AND S. J. KEENS

SUMMARY

During an attempt to measure renal function during operation in six patients undergoing major abdominal surgery involving intestinal resection and blood loss in excess of 300 ml, it became apparent that the conventional recommendation for i.v. crystalloid fluid of 5–10 ml kg^{-1} h^{-1} was not sufficient to maintain cardiovascular stability and urine output, but a volume of 15 ml kg^{-1} h^{-1}, given to a subsequent six patients, was adequate. Administration of low sodium (glucose) solutions also produced biochemical abnormalities of a severity not documented previously. A survey of the published literature on volumes of crystalloid fluids used supports the contention that, during major surgery, crystalloid requirements may be of the order of 10–15 ml kg^{-1} h^{-1} rather than 5–10 ml kg^{-1} h^{-1}.

KEY WORDS

Fluid balance: i.v. crystalloids, intraoperative fluids. Surgery: abdominal.

Crystalloid solutions are normally given during surgery (in addition to replacement of significant blood loss) to maintain cardiovascular stability and urine output. The literature on this subject recommends a volume of 5–10 ml kg^{-1} h^{-1} for a desirable urine output for the average adult of 30 ml h^{-1} [1–7]. Some authorities recommend only "balanced salt solution," such as Hartmann's, or saline [2, 4, 5, 7]. Some recommend isotonic (5%) glucose followed by Hartmann's solution [3], whilst others recommend iso-osmotic mixtures of glucose and saline [6]; recently there has been a move to restrict the volume of infused crystalloids by use of colloids [8].

During a recent attempt to measure renal blood flow and glomerular filtration rate during major abdominal surgery (i.e. surgery involving intestinal resection and a measured blood loss in excess of 300 ml) in which crystalloids were given at the recommended rates, it became apparent that these recommendations were inadequate, and that the biochemical abnormalities produced by infusing 5% glucose or 0.18% saline–4% glucose were more severe than had been realized previously. Largely because of the problems to be described in this report, the renal measurements are unfortunately not available, but the consequences are presented here of infusing crystalloid solutions (in addition to replacement of measured blood loss), high and low in sodium concentration during major surgery in 12 patients at rates of 10 and 15 ml kg^{-1} h^{-1}.

PATIENTS AND METHODS

Twelve patients devoid of cardiovascular and renal disease (no cardiac abnormalities detectable on clinical examination, ECG or chest x-ray, a normal plasma creatinine and taking no medication) gave consent. The study was approved by the local Ethics Committee.

Patients were allocated randomly to receive 5% glucose or Hartmann's solution 10 ml kg^{-1} h^{-1} during operation. For the renal study, they received 4% glucose–0.18% saline 1000 ml i.v. during the 60 min before induction of anaesthesia [9]. With the first six patients it became apparent that 10 ml kg^{-1} h^{-1} did not maintain arterial pressure and urine output (see later), so the

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second six patients received 15 ml kg^{-1} h^{-1} as Hartmann's solution or 0.18% saline–4% glucose. After operation, all were given 0.18% saline–4% glucose 1.8 ml kg^{-1} h^{-1}.

A radial artery cannula and urinary catheter were inserted. A bolus of inulin and PAH was given (for the renal study), and inulin and PAH in whatever fluid the patient was to receive during operation, infused at 240 ml h^{-1}. After 25 min, urine output was measured for 15 min, the patient anaesthetized and urine output measured for a further 15 min. Intraoperative fluids were then commenced at a rate to provide a total, in combination with the 240 ml h^{-1} being given, of 10 or 15 ml kg^{-1} h^{-1}.

Anaesthesia was induced with thiopentone followed by pancuronium i.v. to facilitate tracheal intubation and muscle relaxation, and morphine was given for intraoperative analgesia. Halothane 0–1% was given as required. At the end of surgery, residual neuromuscular block was antagonized with neostigmine. Morphine was used i.m. for postoperative analgesia. Drugs were given as judged clinically and the dose recorded. Every 30 min during surgery and every 1 h for 5 h after operation, urine volume and urinary sodium were measured and arterial blood analysed for $P\text{CO}_2$, glucose and sodium concentrations and osmolality.

Blood loss was measured by weighing all swabs and measuring wound suction. When losses totalled 600–700 ml, blood transfusion was commenced and a minimum of 2 units of fluid given, the first unit being whole blood and all units thereafter "plasma reduced".

RESULTS

For the purpose of analysis, the 12 patients have been classified into two groups in two ways: one classification according to the volume of fluid (i.e. 10 ml kg^{-1} h^{-1} or 15 ml kg^{-1} h^{-1}), so that the two groups of six patients each consisted of three who received high sodium solutions and three who received low sodium (glucose) solutions, and the other according to the type of fluid, so that of the two groups of six (high and low sodium (glucose)), each consisted of three who received 10 ml kg^{-1} h^{-1} and three who received 15 ml kg^{-1} h^{-1}. The details are not presented, but under both classifications each of the two groups were comparable for age, body mass index, blood loss, blood transfused, anaesthetic drug doses and duration and extent of surgery. Surgery lasted for between 104 and 189 (median 134 min). Data for all patients have been analysed therefore, over the first four 30-min periods of surgery and over the 5 h of the recovery period.

Clinical details

In two patients receiving 10 ml kg^{-1} h^{-1}, the procedure had to be modified because of clinically unacceptable hypotension and oliguria (systolic arterial pressure < 90 mm Hg for 10 min and urine output < 10 ml h^{-1}). One was receiving Hartmann's solution, the other 5% glucose. Both were given an extra 1 litre of Hartmann's solution; one received 500 ml during the last 15 min of surgery and a further 500 ml during the second 1 h of the recovery period. The other patient was given 1 litre of Hartmann's solution during the fifth hour of recovery. A third patient became acutely hypotensive and oliguric that evening. In the absence of further blood loss, he was resuscitated with Hartmann's solution. All patients receiving 15 ml kg^{-1} h^{-1} maintained a satisfactory arterial pressure and urine output throughout the operation and recovery period.

Arterial pressure, urine output and Pa_{CO_2}

There were no differences in arterial pressure between the patients receiving glucose or Hartmann's solution either during surgery or after operation. When patients were classified according to the volume of fluid, mean arterial pressure (MAP) over the first 30 min of surgery was 100 (7) mm Hg (mean (SEM)) in the 10-ml kg^{-1} h^{-1} group and 102 (7) mm Hg in the 15-ml kg^{-1} h^{-1} group. In the latter group this was maintained, but in the 10-ml kg^{-1} h^{-1} group, MAP over the second 30 min decreased to 85 (7) mm Hg. Over 60–90 min, MAP was significantly lower in the 10-ml kg^{-1} h^{-1} group than the 15-ml kg^{-1} h^{-1} group (82 (6) mm Hg *vs* 99 (6) mm Hg) ($P < 0.05$) and over 90–120 min this difference increased (79 (4) mm Hg *vs* 105 (5) mm Hg) ($P < 0.01$). During surgery, urine output was significantly greater in the patients receiving fluid at 15 ml kg^{-1} h^{-1} than at 10 ml kg^{-1} h^{-1} ($P < 0.05$) and greater in the group receiving glucose than the patients receiving Hartmann's solution ($P < 0.01$). The median rate of output of urine in the Hartmann's group during surgery was less than 0.5 ml min^{-1}, but in the patients receiving glucose it was always greater than 1 ml min^{-1}. During operation, sodium excretion in the patients receiving glucose was 18.0 (7.1) mmol, comparable to that in the post-operative period (23.9 (7.0) mmol). Sodium excretion in the patients receiving Hartmann's solution was 6.8 (2.7) mmol during operation and this increased five-fold to 35.2 (8.5) mmol after operation ($P < 0.01$).

Blood concentration of glucose during infusion of glucose increased to mean 23.0 (SD 4.6) mmol litre^{-1}. One patient had an osmotic diuresis (urine output greater than 12 ml min^{-1} and 3+ glucose in the urine when tested with Labstix (Ames Laboratories, Slough)). Two other patients receiving glucose had 1+ glucose in the urine, but no evidence of a diuresis. No glycosuria occurred beyond the first 1 h of recovery. Blood concentration of glucose at 5 h was comparable to that in patients receiving Hartmann's solution. Plasma concentration of sodium in the Hartmann's group remained within 1–2 mmol of the value before operation, but decreased to mean 117 (SD 5) mmol litre^{-1} in the patients receiving glucose. It remained in the range 117–123 mmol litre^{-1} for 5 h after operation and throughout the postoperative period was significantly less than the range of 135–138 mmol litre^{-1} seen in the patients who had received Hartmann's solution ($P < 0.01$). The day after surgery the plasma concentration of sodium in the patients who received Hartmann's solution was 133 (SEM 1) mmol litre^{-1} and that in the glucose group 130 (1) mmol litre^{-1} (ns). Mean plasma osmolality remained about 280 mosmol kg^{-1} in the Hartmann's group, but decreased during operation to about 270 mosmol kg^{-1} in the patients receiving glucose and decreased further after operation, to 255–260 mosmol kg^{-1}. There was no difference in Pa_{CO_2} (which has profound effects on both cardiac output [10] and on urine flow [11]) between groups in either of the classifications, either during surgery or after operation. Pa_{CO_2} was generally in the range 4.3–4.8 kPa and after operation 5.1–5.3 kPa.

DISCUSSION

This report provides only some preliminary information, so any conclusions must be tentative. There were only 12 patients, the fluid regimens were not given in random order and the investigators were not blinded to either the type or the volume of fluid administered. In contrast, crystalloid was given by infusion pump and the infusion rates were not altered, extra Hartmann's solution being given separately over relatively short periods. This report derives from an attempt to measure renal function during and after surgery; in part this failed, because the conventional recommendations for intraoperative fluid replacement did not maintain arterial pressure and urine output, despite a preoperative fluid load of 1240 ml. It also shows that giving fluid as low sodium (glucose) solutions in volumes large enough to maintain cardiovascular stability and urine output produced degrees of hyponatraemia and osmolality that have not been reported hitherto and are probably unacceptable. On the other hand, urine output was greater during operation with glucose than with Hartmann's solution. There were large differences in patterns of sodium excretion; these probably reflect the effects of the different sodium loads and osmolalities on aldosterone and arginine vasopressin (antidiuretic hormone) secretion, but in the absence of any hormone measurements this is speculative.

Views on what fluids should be given during operation have varied over the years, from Moore's contention that sodium was retained during and after surgery so its administration should be restricted [12] to the concept of Shires, Williams and Brown of a "third space" and the need to fill it with balanced salt solution [13]. In an attempt to reduce the volume of fluids given during operation, colloids have been advocated in place of crystalloids [8]. The preliminary observations presented here suggest that, if crystalloids are given during major surgery, the requirement may be 10–15 ml kg^{-1} h^{-1} and not 5–10 ml kg^{-1} h^{-1}. This is more than any other published recommendation, and is 50% greater even than that recommended by Shires' group [13] and, in view of the danger of pulmonary oedema, might be considered excessive. However, several papers that have recorded volumes of fluid given during major surgery have produced similar values. Shires and colleagues [14] reported 1123 (449) ml h^{-1} with surgery lasting 4.8 h, Slotman, Jed and Burchard 1100 ml h^{-1} [15] and Virgilio and colleagues 1161 ml h^{-1} [16]; assuming a body weight of 70 kg, these volumes correspond to 16 ml kg^{-1} h^{-1}. Roberts and co-workers reported even greater values—24 ml kg^{-1} h^{-1} [17]. In two of these studies [14, 17], extravascular lung water and extracellular fluid volume were measured and did not change from the preoperative value, so 15 ml kg^{-1} h^{-1} may not be an unreasonable figure.

The use of colloids during operation has been reported by Shires and colleagues [14] to reduce the volume of fluid given during operation by 50%, but postoperative urine output also decreased by 50%. This may be considered undesirable because of the danger of renal failure. Teleologically, fluid retention at the time of injury (perhaps by sequestration in "third space") serves as a reservoir from which urine output may be maintained after injury when the ability of an organism to forage for food and drink is impaired [18–20]. In two studies, restriction of intraoperative crystalloid and replacement only of blood loss resulted in a plasma volume deficit after operation [17, 21]. Perhaps administration of fluid during operation should be designed to fill up the "third space", as suggested by Shires [14], the appropriate volume to achieve this being 10–15 ml kg^{-1} h^{-1}.

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CORRESPONDENCE

EXTRADURAL PETHIDINE

Sir,—We were interested to read the recent paper by Perriss, Latham and Wilson comparing extradural pethidine 50 mg with i.m. pethidine 100 mg after Caesarean section [1]. The summary states that the extradural route provided superior analgesia; the results, as presented, do not support this conclusion. "Superior" may mean faster onset, greater effect, longer duration or fewer side effects. The authors tell us that there were no significant differences between the groups for duration of effect, number of doses required or incidence of side effects. The difficulty for the reader then is to judge whether the claimed superiority is in faster onset, greater effect, or both.

Dr Perriss states "the onset of pain relief with extradural pethidine was faster...presumably because it was delivered close to its site of action". Pethidine applied directly to the spinal cord takes 20 min to block activity in dorsal horn nociceptive neurones [2]. A rapid onset of action would suggest, therefore, that the effect was not through the spinal opioid receptors and, indeed, figure 1 shows that times to significant analgesia (15 min) and to maximum analgesia (20 min) were the same in the i.m. and extradural groups. The data are confusing because the initial pain scores are so different (?significantly) in the two groups and because the statistical analysis compares each group with its own baseline (which demonstrates merely that analgesia was achieved) rather than with each other.

Was there a significant difference in the analgesic effect between the two routes? Figure 1 does not allow us to judge this because the statistical analyses are made *within* groups rather than *between* groups. The only mention which we find is that "pain scores in the extradural group were always significantly lower at 30 min". Lower than what—the baseline scores or the i.m. group? This key issue is not illuminated by the subsequent text.

The "weak local anaesthetic properties" of pethidine referred to in the final paragraph rather undervalue the fact that intrathecal pethidine in a dose of 0.5 mg kg^{-1} as a 5% solution provides anaesthesia comparable to that of bupivacaine or lignocaine and lasts for 2 h [3]. An extradural local anaesthetic action may explain lower pain scores in the extradural group, particularly if measurements were taken on movement rather than at rest.

"Spinal opioid" is a term used to describe both the extradural and intrathecal routes of administration for opioid drugs. Local anaesthetics require different terminology because they may act at both sites: extradural nerve roots (extradural local anaesthetic), or the cord and cauda equina (intrathecal or spinal anaesthetic). However, although the same term is used for extradural and intrathecal opioids, this does not guarantee that the sites of action are the same. There is evidence that this is not the case, especially with lipid soluble drugs such as pethidine, fentanyl and buprenorphine.

The authors state that pethidine and other lipid soluble drugs have a rapid onset of action when given extradurally. They may indeed act quickly, but this is much more likely to be a result of systemic uptake rather than dural transfer leading to a spinal effect. Moore and colleagues showed that transfer of opioids across the dura varied, not with lipid solubility, but inversely with the square root of molecular size [4]. They did not study pethidine, but its molecular weight suggests that 2% of a dose would cross the dura; the figure for morphine is 20%—a 10-fold difference. After crossing the dura, the drug may act on receptors in the spinal cord. Potency is inversely related to lipophilicity [2]. Pethidine is more lipophilic than morphine and so less potent when given intrathecally; the ratio morphine to pethidine is again 10:1.

Combining the results of these studies, 10% of the amount of pethidine crosses the dura compared with morphine, where it acts on the cord to produce 10% of the analgesic effect of morphine. Pethidine given extradurally therefore has 1% of the potency of extradural morphine. Pethidine 50 mg given in Dr Perriss' study is equivalent to 0.5 mg of extradural morphine. The usual extradural dose of morphine is 2–10 mg. Therefore, Dr Perriss has not given his patients an effective spinal dose of pethidine.

Figures for extradural fentanyl show that it is about twice as potent as morphine, so that a standard dose of extradural fentanyl would need to be 1–5 mg to achieve an effect [5]. This is reinforced by Loper's trial comparing extradural against i.v. fentanyl for postoperative analgesia. The effect of an extradural infusion of 100 μg h^{-1} was indistinguishable from 100 μg h^{-1} i.v. Pain scores at rest and with movement, side effects and plasma fentanyl concentrations were identical in the two groups [6]. This suggests that the extradural infusion was acting systemically not spinally, and no additional benefit is conferred by extradural delivery.

If doses are based on i.v. or i.m. potencies, then extradural pethidine is no more than an exotic way of giving an i.m. injection. Despite the proximity of the drug to the dorsal horn opioid receptors, the effect is through systemic absorption not through spinal mechanisms. The marginally quicker uptake is not enough to justify the dangers, inconvenience and additional cost of the extradural route over an i.m injection.

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Sir,—Thank you for the opportunity to reply to Drs Nagle and McQuay, who question whether we have shown that extradural pethidine provides analgesia superior to that of i.m. pethidine.

We should point out that our original submission was a full length paper that was accepted only on the basis that it appeared in the form of a short communication. Many of Drs Nagle's and McQuay's queries would have been answered had it not been for the necessary reduction in the number of figures and the length of the discussion.

Figure 1 of our paper shows that the time to significant analgesia differed between the extradural and i.m. groups, being 5 and 15 min respectively, although maximal analgesia was achieved in both groups at about 25 min. Although the initial pain scores were different, they were not significantly so, and were a result, presumably, of an effect of chance in the randomization procedure. There were 14 patients in the extradural group and 16 in the i.m. group. When pain scores were compared between the groups, there was no statistical difference at baseline, 5 or 10 min after treatment. However, at 15 min and at all observations thereafter there were significant differences in pain scores between the two groups ($P < 0.01$). The figure was based on the results of the first "on demand" treatments. On subsequent demands pain scores were taken before and 30 min later only. The greater numbers involved in all on demand extradural top-ups (65) *vs* all on demand i.m. injections (72) provided better statistical comparison of the two techniques. No difference in pain scores was demonstrated before on demand treatment, but at 30 min, scores in the extradural group were always lower than in the i.m. group ($P < 0.001$).

We do not understand the comment made about the weak local anaesthetic properties of pethidine 0.5 mg kg^{-1} (35 mg) intrathecally—a dose associated with anaesthesia and analgesia. This is equivalent, on Drs Nagle's and McQuay's own admission, to pethidine 350 mg given extradurally. Pethidine 50 mg extradurally is therefore likely to be associated with only weak effects. However, we are happy to concede that this may contribute to its superior analgesic effect and possibly to a reduction in the incidence of side effects.

Much has been written on the superior analgesic effect of extradural pethidine being a result of high systemic blood concentrations following rapid absorption of the drug. Husemeyer and colleagues [1] showed that pethidine 100 mg extradurally produced twice the blood concentrations as pethidine 100 mg i.m., and argued that the superior analgesia of the extradural route was caused by this effect. We have compared pethidine 50 mg extradurally with 100 mg i.m. This produced similar blood concentrations, yet analgesia following extradural pethidine was superior. The effect, therefore, cannot be caused solely by systemic action.

The work of Moore and colleagues [2] on the transfer of opioids across the dura *in vitro* does not accord with *in vivo* work in humans. Sjöström and colleagues [3], following morphine 3 mg or pethidine 30 mg extradurally have shown that peak concentrations of morphine are not seen in the CSF for 60–90 min, whilst peak concentrations of pethidine occur in 15–30 min, corresponding to the time of maximal pain relief with these drugs. Furthermore, only 3.6% of the extradural dose of both pethidine and morphine reaches the CSF. This is significantly different from the point made by Nagle and McQuay that only 10% of pethidine crosses the dura compared with morphine, as calculated from *in vitro* studies. We suspect the difference between the *in vitro* and *in vivo* situation is that which has been suggested by Cousins and Mather [4]—that drug is transported from the extradural space to the CSF via the spinal radicular vessels, and the amount transferred in this way is related to its lipophilicity. Sjostrom and colleagues [3] showed that equivalent intrathecal doses of morphine and pethidine are 0.25 mg and 2.5 mg, which supports McQuay's work on the inverse relationship between potency and lipophilicity. It also suggests that, on the basis of a 3.6% dural transfer of morphine and pethidine, the effective extradural dose of pethidine is 70 mg, not 200–1000 mg as suggested by Nagle and McQuay.

There is no doubt in our minds that extradural pethidine gives superior analgesia of faster onset than i.m. pethidine, and that this is the result of a combination of local action on the spinal cord and a systemic effect. We would argue, however, against extradural pethidine being an exotic way of giving an i.m. injection. If an extradural catheter has been inserted as part of one's anaesthetic technique, why not use it to provide postoperative pain relief? With the experience of some 8000 doses of extradural pethidine administered at this hospital since 1979, we can testify to its effectiveness and safety.

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EXTRADURALS AND SHIVERING

Sir,—We were interested in the study by Drs Ponte and Sessler [1] as their results are broadly in concordance with ours. They concluded that the contribution of the anaesthetic temperature to shivering in their four non-pregnant subjects was minimal.

We investigated the link between shivering and cooling of the extradural space in 12 pregnant women at term about to undergo elective induction of labour or Caesarean section. None of the patients shivered after injection of 0.9% sodium chloride 10 ml at 4 °C given over 15 s. Twenty minutes later, extradural block was instituted with 0.5% bupivacaine with adrenaline at ambient temperature, and two of the patients subsequently shivered.

We would agree, therefore, that local anaesthetic facilitates shivering, but disagree that this response is altered substantially in pregnancy. Indeed, in the author's earlier study [2], the incidence of shivering was merely reduced and not abolished after warming the bupivacaine, and an earlier study [3] also had failed to demonstrate any benefit from warming the local anaesthetic.

Our study was abandoned after three of our patients complained of discomfort on injection; we were surprised to see that Ponte and Sessler's volunteers tolerated an injection volume of 80 ml given at a greater rate!

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SIR,—Drs Wenstone and Hardy's interesting preliminary experiments contribute to, but do not resolve, the discrepancy between the findings in non-pregnant and pregnant subjects. The results of our previous paper in pregnant women which showed a different incidence of shivering with warm and cold bupivacaine suggest that pregnancy may potentiate the effect of cold extradural injections. Drs Wenstone and Hardy's procedure should include the blind injection of warm and cold saline in larger volumes, monitoring of body and room temperatures, and a larger number of subjects.

Unless the pregnant subjects are brought close to the shivering threshold by placing them in a cool environment during the tests, the effects of cold injections may not be elicited.

The authors are reasonably sure about the lack of major discomfort on injection of 80 ml saline because they tried it on themselves!

J. PONTE
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BOOK REVIEW

A Practice of Cardiac Anaesthesia, 1st Edn. Edited by F. A. Hensley jr and D. F. Martin. Published by Little, Brown & Co., London. Pp. 759; indexed; illustrated. Price £16.00.

This is a useful book as an addition to the range of text books on cardiac anaesthesia. It consists of 24 chapters written by 37 contributors and is divided into three sections.

The first section, Anaesthetic Management for Cardiac Surgery, contains 10 chapters and discusses the standard anaesthetic management from preoperative assessment of the patient through the operating room, drugs, monitoring, induction and management during the procedure including the cardiopulmonary bypass periods, and ends with a chapter on the first 24 h after operation.

The second section, Anaesthetic Management for Specific Cardiovascular Disorders, consists of eight chapters discussing management for revascularization, congenital and valvular heart disease and cardiac transplantation. It also has valuable chapters on management of thoracic aneurysms and dissection, which will be useful especially for this increasing problem, and a chapter on anaesthesia of patients with electrophysiological disorders—again, an increasing problem. There is also a chapter on Coagulation Management in the Cardiac Pulmonary Bypass Patient.

The third section, Mechanical Support of the Circulation, comprises six chapters on cardiopulmonary bypass circulatory assist devices and membrane oxygenation. It also includes a chapter on brain protection during cardiac surgery, one of the areas which is undergoing more evaluation.

This book is aimed at the trainee anaesthetist and will prove valuable as a working book and library text. It is written clearly and each chapter has good references, in addition to suggested further reading. Each chapter also has a sectional guide. The illustrations are quite clear, but some suffer from not being associated with the relevant page of text. The book will also provide a valuable training manual from which the trained cardiac anaesthetist can teach, especially in the operating room environment. The two Editors are to be congratulated on putting together such a valuable text.

I. McLellan

Primary Surgery — Volume 1 — Non Trauma. By M. King, P. Bewes, J. Cairns and J. Thornton. Published by Oxford Medical Publications, Oxford. Pp. 640; indexed; illustrated. Price £15.00

This is a fascinating book written by several doctors and surgeons who have worked overseas. The book is aimed at those doctors who have to work in conditions in which all the facilities that we have come to accept as normal and the specialties associated with them are not available. The book was sponsored by the German Federal Ministry of Economic Co-operation with the Kenyan Government and the authors have done a tremendous job in putting together in this volume a comprehensive approach to surgical problems as they might be seen in under-developed countries.

This does not imply that it is not well produced or extremely useful. It has several excellent illustrations and contains not only background information, but a wealth of practical details, from taking out pieces of bowel, stones and exposing arteries, to incising an abscess. In addition, it crosses specialty boundaries, describing details of techniques in dental surgery, ENT, gynaecology and general surgery in addition to obstetrics. Not only are various operations described, but the instruments necessary for various procedures are listed at the back of the book, together with the name of the supplier. Trauma is not mentioned in this particular issue but will be the subject of another volume. Anaesthesia is described in detail, even to a situation in which an anaesthetist may not be available and the surgeon has to do both the operation and the anaesthetic!

The book is not referenced, but references are not appropriate for this type of presentation. It is very reasonably priced at £15 and perhaps its only drawback is that it is not for the poor sighted as the print is quite small.

Although this admirable book has been produced for the doctor or surgeon working in a situation in which there are no specialists or facilities are limited, those working in more privileged environments would still find it extremely useful. I am sure it will be very successful in so-called third world countries, but it would not be out of place on the bookshelf of the modern general surgeon. At this price one can hardly afford to miss it.

P. E. F. Bell

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

DEVELOPMENTS IN THE SAFE USE OF HIGH FREQUENCY JET VENTILATION

The prevention of hypoxia is obviously fundamental to anaesthesia, but the classification of our specialty by the defence organizations as "high risk" would suggest that we occasionally fall short of this objective. While few would dispute that anaesthesia is inherently dangerous, one wonders if the psychological profile of anaesthetists predisposes them to take risks unnecessarily, or to accept perceived risks with equanimity, in order to maintain an image of confidence or ability [1].

Anaesthesia in patients with airway obstruction from whatever cause is undoubtedly one of the greatest hazards in clinical anaesthetic practice. When the airway must be shared also with the surgeon, the risks taken may be considerable. The ignition of tracheal tubes by lasers may be prevented only by a damp swab, or surgery may be performed on an apnoeic patient without a tracheal tube. Patients with a trachea known to be difficult to intubate may be given an i.v. induction, the possibility of obstruction being accepted. The patient with epiglottitis may receive an emergency tracheostomy, having obstructed during an attempted anaesthetic induction and tracheal intubation. Why do these potentially lethal events still occur?

The use of high frequency jet ventilation (HFJV) in airway surgery is now well established [2–4]. Its unique ability to deliver tidal volumes via a narrow cannula, which may be inserted under local anaesthesia, either via the pharynx or by direct tracheal puncture, may greatly increase patient safety in maintenance of oxygenation and reduction of ignition hazards [4]. HFJV may be used to ventilate the lungs without the necessity for an airtight seal; this may not only help the surgeon, but may also increase patient safety if the airway is inadvertently breached [5–6] and in ball-valve obstruction. It may even obviate the need for cardiopulmonary bypass [7].

In the face of such advantages, why have techniques utilizing HFJV not become standard practice? After 15 years of clinical use, it should not be lack of understanding of HFJV that has inhibited its widespread adoption. Despite the almost universal use of the Sanders injector as a low frequency jet ventilation system, the ventilatory frequencies used in HFJV seem to alarm anaesthetists. This is curious because, while high frequencies may occasionally cause problems, it is the pressures involved that are the main hazard to the patient.

HFJV entails the use of gases at pressures of 25–400 kPa. Whilst it is true that the tidal volume may be only 2–3 ml/kg body weight, 200 ml of gas delivered into the wrong location can cause serious problems; this is compounded by the ventilation frequency which varies typically from 60 to 180 b.p.m. Assuming that a patient is checked every 10 s, and assuming that a problem was diagnosed and the ventilator turned off within a further 5 s, as much as 8–12 litre of gas could have been delivered. In a patient with outflow obstruction this volume would lead to barotrauma and cardiac compromise. A recent report [8] has highlighted these dangers and shown also that similar hazards occur with the use of manually operated Sanders injectors which, because they are used at low frequencies, require correspondingly high tidal volumes.

If barotrauma is to be avoided, the system of ventilation must use small tidal volumes and rapid response ventilators, which incorporate appropriate airway pressure sensing devices with immediate inhibition of gas delivery following activation of these sensors. High frequency jet ventilators exploiting these features have been available for several years. While this method is certainly effective and has been recommended in prevention of increased airway pressures [8], there is an alternative solution. In the past it has always been necessary to introduce a second catheter into the airway for the airway pressure monitor. While this need be only a fine-bore cannula, it is still inconvenient. An elegantly simple solution to the second cannula problem has been developed by Bourgain's group and is reported in this issue [9]. They have developed the GR 300 ventilator which uses the main gas delivery line for airway pressure monitoring. The airway pressure is recorded from the main injection cannula at the end of expiration—the end-expiratory pressure (EEP). Failure of EEP to decrease below a user-selected preset limit inhibits the next ventilatory cycle. In practice, this not only prevented the build up of dangerously high airway pressures, but also gave warning that airway obstruction was beginning to occur as the ventilator demonstrated "missed beats".

The use of both methods of airway pressure monitoring should reduce the incidence of barotrauma, but there is still the problem of initial misplacement or subsequent displacement of the cannula resulting in paratracheal delivery. Even the sophistication of the GR 300 could not prevent this. Ideally, the ventilator should be able to detect resistance to gas delivery before supplying even the first tidal volume.

Preliminary data from one manufacturer would appear to show that this difficulty may soon be overcome. In a new approach to this problem, a low flow (250 ml min^{-1}) of gas at low pressure (< 4 kPa) is passed through the injection cannula between the main gas pulses and measures the expiratory airway pressure. Unacceptably high EEP inhibits the ventilator (as before), but misplacement of the cannula in the paratracheal tissues produces back pressure in the delivery line caused by the low flow system, which cannot exceed 4 kPa, and may be set as low as 1 kPa. This inhibits gas delivery by both the main ventilator and the low pressure system itself. Initial results suggest that the system activation time limits the volume of gas in the paratracheal tissues to as little as 3–5 ml [Technical Department, Penlon U.K., personal communication].

Through technological advances, the design of modern ventilators has now achieved an unprecedented level of safety. One assumes that the adapted, home made or "prototype" ventilators which lack such essential refinements will be abolished, whilst HFJV using safe ventilators will become a standard method of anaesthetic management in cases of airway obstruction and airway surgery. If we are to provide our patients with maximum safety, we can offer no less.

B. E. Smith

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MEASUREMENT OF END-EXPIRATORY PRESSURE DURING TRANSTRACHEAL HIGH FREQUENCY JET VENTILATION FOR LARYNGOSCOPY

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SUMMARY

*An anaesthetic technique using high frequency jet ventilation has been proposed for direct laryngoscopy, but this may expose the patients to the risk of barotrauma. In order to assess this risk, we have measured end-expiratory airway pressure (EEP) through the injector using two three-way solenoid valves mounted in series. At the end of insufflation the first valve was switched off and the apparatus deadspace connected to atmosphere through a large exit port during an adjustable time (decompression time). Then the second valve was switched off and the injection line connected to a transducer, allowing measurement of EEP through the injector. The accuracy of this measurement was tested against airway pressure measured directly in the trachea (*Pt*) in a lung model. Provided that the decompression time was long enough (70 ms) and the apparatus deadspace was small (6 ml), the difference between EEP and* Pt *was less than 1 cm H_2O for frequencies up to 5 Hz. A clinical evaluation was performed in 64 patients under general anaesthesia before laryngoscopy. EEP correlated with end-expiratory pulmonary volume above apnoeic FRC inferred from abdominal and thoracic displacements. At jet frequencies up to 5 Hz, the correlations between these two variables were satisfactory (*$r > 0.88$*), suggesting that EEP is a good indicator of pulmonary overdistension.*

KEY WORDS

Ventilation: high frequency jet, transtracheal. Monitoring airway pressure.

High frequency ventilation (HFV) has been proposed as an alternative to conventional ventilation for laryngoscopy under general anaesthesia [1]. Different methods of tracheal access have been suggested: nasotracheal, orotracheal and transtracheal [2–5]. The cricothyroid membrane catheter is particularly interesting because it avoids intubation manoeuvres. Potential hazards of jet ventilation include barotrauma with subcutaneous emphysema, pneumomediastinum or pneumothorax [6–8]. The risk of barotrauma may be greater in patients with upper airway obstruction, a condition which is frequently found in patients requiring laryngoscopy.

Detecting hyperinflation is difficult when the trachea is not intubated; it involves either measurement of airway pressure or external spirometric methods [9, 10]. External spirometric methods possess technical and methodological difficulties in terms of linearity, frequency response and calibration [11].

Mean airway pressure has been reported to correlate well with mean pulmonary volume during high frequency jet ventilation (HFJV) [12], but its measurement requires the use of a special intratracheal cannula which may be inconvenient when the trachea is intubated with a small tracheal tube, or when HFJV is delivered via a transtracheal catheter. Measurement of

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This article is accompanied by an Editorial.

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airway pressure is possible via the injector at the end of expiration and if the end-expiratory pressure (EEP) is a good reflection of pulmonary distension, this would be a useful manoeuvre.

The aim of this study was to evaluate: the difference between EEP measured via the injector and through a tracheal catheter in a lung model; the accuracy of EEP as a reflection of pulmonary distension during HFJV in patients undergoing direct laryngoscopy; and the reliability of a device to stop the ventilator automatically when EEP reaches a preset value in order to avoid pulmonary distension.

METHODS

EEP measurement

The ventilator used (GR300, LSA, France) operated as described by Carlon and colleagues [13]. This device is solenoid operated and the electronic clock allows independent setting of ventilatory frequency and inspiratory:expiratory (I:E) ratio. The unique feature of this ventilator is the measurement of airway pressure through the injector catheter between each insufflation. Two three-way solenoid valves in series are used for this purpose (fig. 1). During insufflation the two valves are open. At the end of insufflation, the proximal valve is switched off and the apparatus deadspace connected to atmosphere. For 70 ms, compressed gas escapes into the atmosphere through a large port and the operating pressure returns quickly to baseline. Then the second solenoid valve is switched off and the injection line connected to a piezoelectric transducer, allowing measurement of dynamic end-expiratory airway pressure (EEP) via the injector. The frequency response of the transducer was flat up to 20 Hz. The technical characteristics of each valve are: internal diameter 3 mm, opening time 12 ms, closing time 17 ms. In case of system failure, valves close automatically.

Each EEP value is recorded by a microprocessor in the ventilator. The microprocessor allows successive inspirations only when EEP is less than a preset value (low mandatory pressure) which may be adjusted from 1 to 30 cm H_2O.

To assess the validity of EEP measurement through the injector, we used a lung model (Manley lung ventilator performance analyser). The static compliance of the lung model was 66 ml cm H_2O^{-1} and the downstream resistance was minimal. The end-expiratory lung volume was 500 ml. EEP was compared with the pressure measured through a tracheal catheter (*P*t), the tip of which was placed 5 cm downstream from the tip of the injector and connected directly to a quartz transducer (HP 1290); the frequency response of the pressure measurement system was flat up to 30 Hz. The driving pressure (3.8 bar), inspired oxygen concentration ($F_{I_{O_2}} = 1$) and I:E ratio (0.54) were kept constant. Five ventilatory frequencies were studied (1, 2, 3, 4 and 5 Hz), three injector diameters (2, 1.7 and 1.3 mm i.d.) and two apparatus deadspaces (6 ml and 1.8 ml). All these settings and designs were tested in two lung configurations: with minimal airway resistance, and with a resistance (8 cm H_2O litre^{-1} s^{-1}) located at the proximal tip of the tracheal tube (to simulate upper airway obstruction).

Clinical study

We studied 64 patients (59 males) aged 59 (SD 9) yr, undergoing endoscopy for upper airway cancer. We excluded patients with contraindications to cricothyroid puncture (local infection, neoplastic extension near the puncture point, anticoagulant therapy) and patients with severe cardiac disease.

The study was approved by our local Ethics Committee and all patients gave informed consent.

Diazepam 0.15 mg kg^{-1} and atropine 0.007 mg kg^{-1} were given i.m. 1 h before laryngoscopy. Anaesthesia was induced with an i.v. bolus dose of propofol 2 mg kg^{-1} or methohexitone 3 mg kg^{-1} in combination with fentanyl 0.10–0.15 mg. Muscle relaxation was produced with vecuronium 0.08 mg kg^{-1}. Anaesthesia was maintained with propofol 10 mg kg^{-1} h^{-1} or methohexitone 7 mg kg^{-1} h^{-1} infused continuously from a syringe pump. Vecuronium was given in intermittent bolus doses of 1 mg when necessary as indicated by monitoring of neuromuscular transmission. After induction of anaesthesia, the cricothyroid membrane was punctured, 2% lignocaine 2 ml was injected and a 14-gauge, 10-cm long catheter (Seldicath, Plastimed France) was inserted into the trachea. Depending on the individual length of the trachea, the tip of the injector was located usually 3 or 4 cm above the carina; this was confirmed by the surgeon during endoscopy in the first patients. HFJV was started immediately. Driving pressure 3.8 bar, $F_{I_{O_2}} = 1$ and I:E ratio 0.54 were kept constant. The internal volume of the connecting tube was 6 ml. The patient's

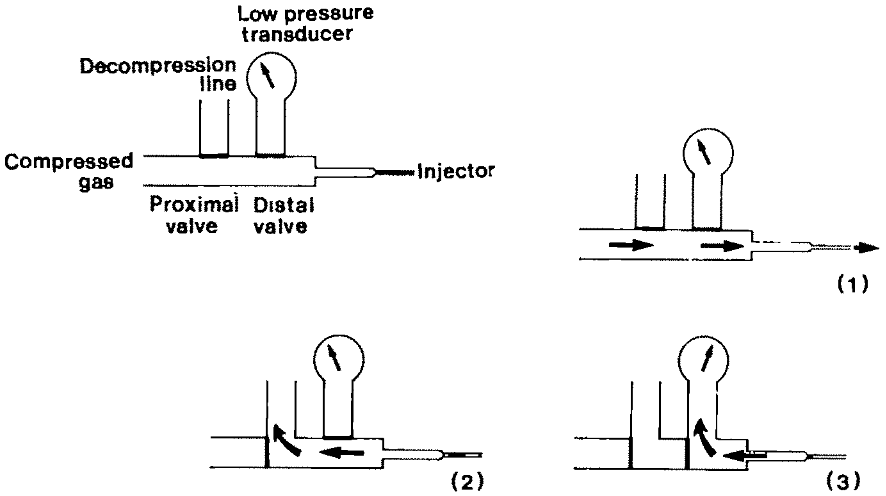

FIG. 1. Mode of operation of ventilator. During insufflation (1), both valves are open. At the end of insufflation (2), the first valve is closed and the gas compressed in the ventilator deadspace escapes. After 70 ms, the second valve is closed and the injector is connected to a transducer allowing the measurement of expiratory airway pressure (3).

trachea was not intubated and airway patency was maintained by lifting the jaw.

Measurements were performed before endoscopy and recorded on an ES1000 Gould chart recorder. To assess changes in pulmonary volumes, two 50-cm mercury strain gauges (LG 500 Sega Electronique, France) were strapped to the patient at nipple and umbilical levels to measure rib cage and abdominal displacements. Frequency response of the strain gauges was flat up to 15 Hz and linearity was satisfactory for displacements smaller than 4 cm (±1%).

The classical method of strain gauge calibration using a syringe could not be used [14], and we therefore used a method derived from that described by Rouby and colleagues [9]. Lungs were insufflated five or six times through the injector for 175 ms at 4-s intervals, with the upper airway occluded firmly by neck flexion and manual closure of mouth and nose. Under these conditions there was no entrained volume and the displacements of the thorax and abdomen were caused only by the injected volume. Simultaneous recording of thoracic and abdominal displacements gave the coefficient of calibration of the two strain gauges by averaging five steps. The presence of leaks was detected easily by absence of a plateau after each step, suggesting incomplete upper airway occlusion. At the end of the study, when the patient was awakened, the injector was connected to a dry spirometer and the injector outflow was measured for 1 min at a frequency of 2 Hz and I:E ratio 0.54 (insufflation time 175 ms). The minute volume was corrected to BTPS conditions and divided by the frequency to obtain the injected volume during the patient calibration procedure. For all patients, the injected volume was found to vary from 105 ml to 122 ml (mean 114 (SD 4) ml).

After the calibration procedure, the study began. Throughout the study, the patients' jaw was lifted forward manually. The ventilatory frequency (1, 2, 3, 4 or 5 Hz) was changed in a random sequence. For each frequency, the thoracic and abdominal pulmonary volumes greater than FRC (dFRC) and end-expiratory pressures were measured after ventilation of the lungs for 30 s.

All data are expressed as mean (SD) and were compared using analysis of variance followed by a modified *t* test and linear regression analysis. $P \leqslant 0.05$ was considered significant.

RESULTS

An example of simultaneous recording of EEP and *P*t is shown in figure 2. In the lung model, injector diameter, volume of the connecting tube

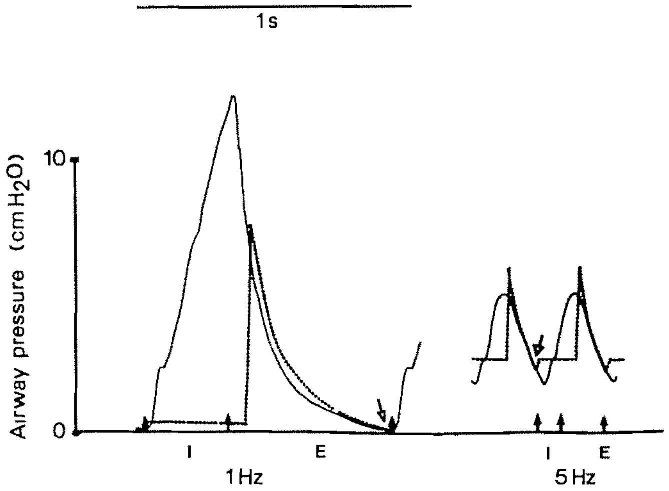

FIG. 2. Simultaneous recording of airway pressure measured directly in the tracheal tube (continuous line) and through the injector catheter during expiration (dotted line) at 1 and 5 Hz (injector diameter 1.7 mm, small deadspace). Measurements were performed at the end of expiration (↓).

and frequency affected the difference between EEP and *P*t (table I). This difference increased when the injector diameter decreased or when the apparatus deadspace increased. Using a 2-mm i.d. injector, this difference was less than 1 cm H_2O, irrespective of frequency or apparatus deadspace. With a 1.7-cm i.d. injector, the difference was greater than 1 cm H_2O at frequencies greater than 3 Hz with the large connecting tube. The difference became appreciable with the 1.3-mm i.d. injector, reaching 5 cm H_2O at 5 Hz with the large connecting tube. The addition of an upstream resistance did not change the gradient between EEP and *P*t (table II).

The dFRC inferred from abdominal displacements correlated well with dFRC inferred from thoracic displacements for all ventilatory frequencies (table III). Correlation coefficients were greater than 0.90 and the slopes were close to the line of identity. Values of dFRC obtained by either thoracic or abdominal gauges were similar. For all patients, EEP correlated well with dFRC measured by either thoracic or abdominal strain gauges (for example $r = 0.90$ and $r = 0.89$, respectively, at 2 Hz) (fig. 3). EEP increased when ventilatory frequency increased while dFRC remained stable. The increase in EEP with frequency was constant in each patient and did not exceed 3 cm H_2O from 1 to 5 Hz (mean 1.7 (SD 1.1) cm H_2O). The individual variations in EEP varied from 0 to 9.4 cm H_2O. Nevertheless, a correlation between dFRC and EEP was present for each frequency and all the correlation coefficients exceeded 0.88 (table III).

The effect of an upper airway obstruction is

TABLE I. *Differences between EEP and* Pt *(cm H_2O) with two sizes of connecting tube, three injector diameters and five ventilatory frequencies, in the lung model*

Connecting tube	Injector diameter (mm)	Ventilatory frequency (Hz)				
		1	2	3	4	5
Large	2	−0.02	0.05	0.3	0.3	0.4
(6 ml)	1.7	0	0.3	0.7	1.1	1.8
	1.3	0.05	1.2	2.3	3.7	5.3
Small	2	−0.1	−0.05	−0.1	0.1	0.1
(1.8 ml)	1.7	−0.1	0.2	0.4	0.5	0.7
	1.3	0	0.4	0.8	1.1	1.6

TABLE II. *Differences between EEP and* Pt *(cm H_2O) after addition of an upstream expiratory resistance simulating an upper airway obstruction in the lung model. These values are similar to those reported in table I*

Connecting tube	Injector diameter (mm)	Ventilatory frequency (Hz)				
		1	2	3	4	5
Large	2	0.1	0	0	0	0
(6 ml)	1.7	0.1	0.2	0.5	0.9	1.4
	1.3	0.05	1.0	2.0	3.2	4.8
Small	2	−0.2	−0.2	−0.3	−0.4	−0.3
(1.8 ml)	1.7	0	0.2	0.2	0.3	0.6
	1.3	0.05	0.5	0.8	1.1	1.5

TABLE III. *Values of dFRC and EEP (mean (SD)) in the 64 patients measured at five ventilatory frequencies using the thoracic (RC) and the abdominal (AB) strain gauges. The correlation coefficient r of the regression lines between dFRC AB and dFRC RC and between dFRC RC and EEP are presented*

	Ventilatory frequency (Hz)				
	1	2	3	4	5
dFRC RC (ml)	162 (180)	191 (173)	190 (157)	182 (147)	161 (139)
dFRC AB (ml)	154 (168)	171 (169)	172 (163)	161 (151)	145 (131)
EEP (cm H_2O)	0.9 (1.7)	1.5 (2.0)	1.9 (2.1)	2.1 (2.1)	2.6 (2.0)
r					
dFRC AB *vs* dFRC RC	0.92	0.95	0.94	0.92	0.90
r					
EEP *vs* dFRC RC	0.94	0.90	0.92	0.88	0.90

shown in figure 4. When obstruction was complete, expiration was not possible. The ventilator insufflated the lungs and both EEP and dFRC increased. When EEP reached the low mandatory pressure, the ventilator could not perform the next insufflation. In case of partial upper airway obstruction, the next insufflation was performed when *Pt* was less than the mandatory pressure. In both situations, EEP could not exceed the preset low mandatory pressure.

DISCUSSION

Measurement of EEP via the injection catheter is a reflection of *Pt* if the gas compressed in the ventilator deadspace escapes completely at the end of the decompression time; for a given decompression time this depends on injector diameter and ventilator deadspace volume. This volume is influenced mainly by the length and internal diameter of the connecting tube. The influence of injector diameter on EEP–*Pt* difference may be explained by the fact that part of the gas compressed in the ventilator escapes through the injector. The larger the diameter, the larger is the amount of gas which escapes through the injector. In our configuration, a decompression time of 70 ms, a ventilator deadspace of 6 ml and a 14-gauge injection catheter were adequate to allow satisfactory measurement of EEP up to 5 Hz. Using the same ventilator in similar patients, satisfactory gas exchange has been obtained with a 2-mm injector, ventilatory frequency 2 Hz and I:E 0.54 ratio [15]. Therefore, the safety margin of EEP measurement was good for injector diameters larger than or equal to 1.7 mm. Obviously, the decompression time must be shorter than the expiratory time and this limit gives the maximal frequency available for a given I:E ratio. As expected, the addition of an upstream resistance did not affect the relationship between *Pt* and EEP.

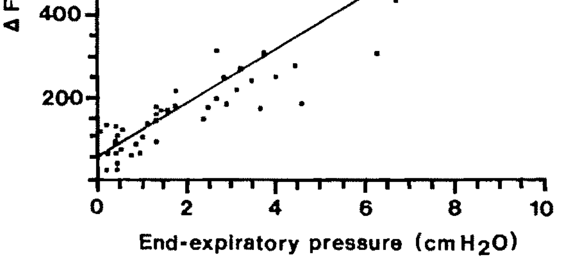

FIG. 3. Regression of dFRC RC and end-expiratory pressure at 2 Hz. To obtain a safety margin, a threshold of 5 cm H_2O may be chosen. Above this limit, most of the patients presented consistent pulmonary overdistension.

During positive pressure ventilation in anaesthetized patients, measurement of lung volumes by external devices depends on Konno and Mead's principle [16]. In such a system, the displacements of each compartment are proportional and the volume inferred from each displacement must be equivalent. This was confirmed in our study, as measurements of dFRC by the two strain gauges were similar.

The use of HFJV has been reported to increase

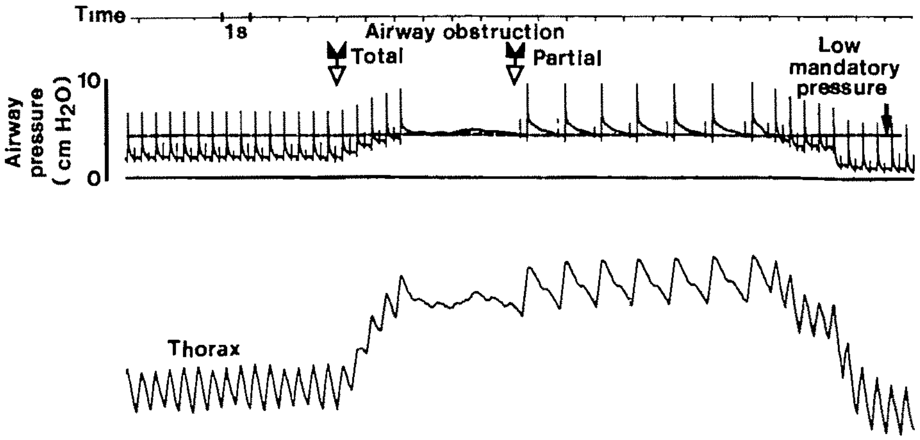

FIG. 4. Simultaneous recording of expiratory airway pressure measured through the injector and thoracic displacement. Low mandatory pressure is represented as a dashed line. When the airway obstruction was complete, end-expiratory pressure increased up to the value of low mandatory pressure. Then, the next insufflation was not performed until the airway pressure was less than the mandatory pressure.

pulmonary volume to greater than the apnoeic FRC [9]. This "PEEP-effect" is primarily a result of intrapulmonary gas trapping. External spirometry has been suggested as a method of monitoring overdistension during HFJV [10]. This procedure requires individual calibration to obtain quantitative measurements, but the calibration procedure is time consuming and requires a computer to calculate changes in dFRC in millilitres. In view of the excellent correlation which we found between dFRC and EEP, it appears that continuous measurement of end-expiratory pressure may be easier and provides a good indication of overdistension at frequencies up to 5 Hz. Similar results have been reported previously in an animal study [17] and in isolated lung [18]. Measurement of EEP did not require individual calibration and the ability to make this measurement through the injector was particularly useful in the absence of a tracheal tube.

The frequency dependence of EEP has been described previously [18]. In our study, it may be related to the increase in gradient between EEP and end-expiratory alveolar pressure. At any frequency, the relationship between EEP and dFRC was present for all patients and the value of EEP may indicate the degree of pulmonary distension. In the presence of bronchial obstruction, there may be a large difference between *P*t and alveolar pressure; in this situation, EEP would not be an accurate guide to pulmonary volume [19]. Further studies are needed in the use of this monitoring in patients with chronic obstructive pulmonary disease.

Control of jet ventilation by the adjustment of EEP may be appropriate in situations which predispose to barotrauma. The system operates during each cycle and allows a quick response to an increase in EEP. In the presence of upper airway obstruction, the risk of increased airway pressure is limited because of decreased ventilatory frequency and minute ventilation (as shown in figure 4), but hypoventilation may develop.

We conclude that, provided certain technical precautions are taken, measurement of EEP through the injection catheter may provide a satisfactory guide to end-expiratory pulmonary volume during transtracheal HFJV. Consequently, continuous monitoring of EEP may detect pulmonary overdistension during laryngoscopy. In the presence of increased airway pressure, the automatic control of ventilatory frequency and minute ventilation reduces the risk of barotrauma, although at the expense of potential hypoventilation.

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ULTRASOUND ASSESSMENT OF THE POSITION OF THE TONGUE DURING INDUCTION OF ANAESTHESIA†

L. J. ABERNETHY, P. L. ALLAN AND G. B. DRUMMOND

SUMMARY

Tongue position was assessed in 15 female patients at induction of anaesthesia with either thiopentone or propofol. A video recording of a midline sagittal section of the tongue was made using an ultrasound transducer placed below the chin, and representative figures analysed by an observer who was not aware of the patient's state. In 11 satisfactory recordings, the tongue movement was inconsistent in direction and not more than 8 mm in the anterior tongue and 6 mm in the posterior tongue. The movements detected did not suggest that the tongue is likely to be an important cause of airway obstruction on induction of anaesthesia.

KEY WORDS

Airway: obstruction, tongue. Measurement techniques ultrasound.

Maintenance of a patent airway is a common and occasionally difficult problem in general anaesthesia. Airway obstruction is often attributed to "falling back" of the tongue [1], resulting in occlusion of the oropharynx, but studies in man and animals indicate that obstruction may be caused in other ways, such as by pharyngeal collapse or by the epiglottis [2, 3]. The present study was undertaken to measure tongue movement during induction of anaesthesia using real-time ultrasound scanning, to assess the likelihood that tongue displacement could cause obstruction.

PATIENTS AND METHODS

This study was a within-subject, observer-blind comparison of tongue movement during induction of anaesthesia. It was approved by the local Ethics Advisory Committee. Fifteen female patients (ASA physical status I or II), who were about to undergo general anaesthesia for minor gynaecological operations, gave informed consent. Each patient was given temazepam 20 mg orally for premedication. Before induction of anaesthesia, the patient relaxed on the trolley with her head in a natural position (not extended) on a single pillow. An i.v. cannula was inserted. A continuous, real-time ultrasound image of the tongue was obtained using a 3.5-MHz mechanical sector-scanning transducer (Siemens Sonoline SX). The transducer was placed below the chin, without altering the position of the head or extending the neck, and positioned to give a good sagittal image of the tongue (fig. 1). The probe was clamped into position with a universal clamp fixed to the trolley, and no further adjustment of the position of the probe was made during the study.

Anaesthesia was induced by i.v. injection of thiopentone or propofol, given over about 30 s, to loss of the lash reflex. The real-time ultrasound image of the tongue was recorded on video, commencing before injection and continuing until at least 1 min after loss of consciousness. Clinical signs of airway obstruction, and the presence of apnoea without ventilatory effort, were noted if possible.

In order to assess tongue movement without observer bias, the images were interpreted in the following way. The video tape recording of the whole sequence was replayed by one observer. Single frames which showed a good image of the whole of the tongue were selected. For each

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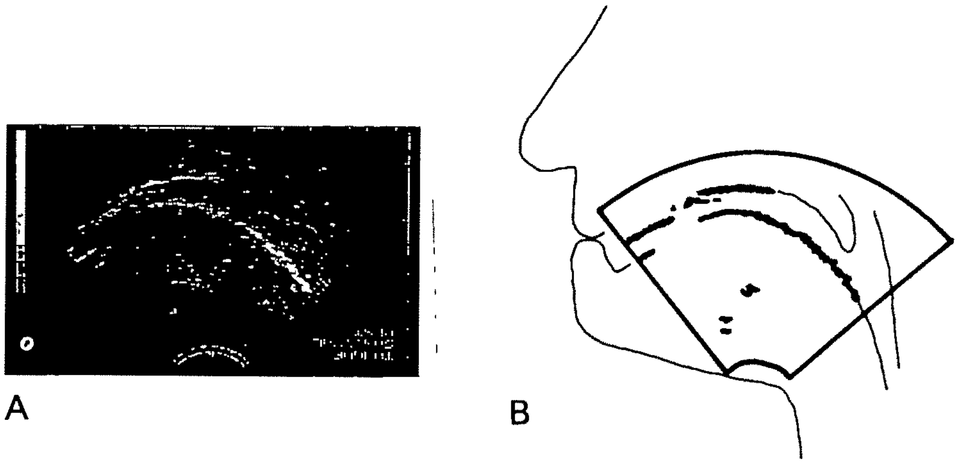

FIG. 1. A: Photograph of sagittal ultrasound image of tongue. The anterior part of the image is on the left. B: Diagram of corresponding sagittal section through the mouth and pharynx showing position of ultrasound image.

patient, two frames were selected before induction and two after induction. If tongue motion was present in phase with ventilation, frames were selected at end-expiration, which could be identified with ease. Photographs were taken of each of these frames, and each pair of photographs for a particular patient in a particular state was given a random code number. The photographs were presented to a second observer, who used each pair of frames to trace a single average outline of the tongue as an arc representing its upper and posterior surface.

Because the tracings for each state were of different lengths of the arc, measurement of tongue movement was made by directly comparing tracings of the images obtained before and after induction. The observer who made this comparison remained unaware of the patient state for each tracing. The common sector along which the tongue surface was identified clearly in both tracings was marked (fig. 2) and measurements made along the radius of the sector to its anterior, middle and posterior points, to the nearest 0.5 mm. The code was then broken, and measurements were related to patient state. Tongue movement was calculated as the difference between radius measurements at each point, and corrected for the scale settings of the imaging system. Data were analysed statistically with binomial distribution [4].

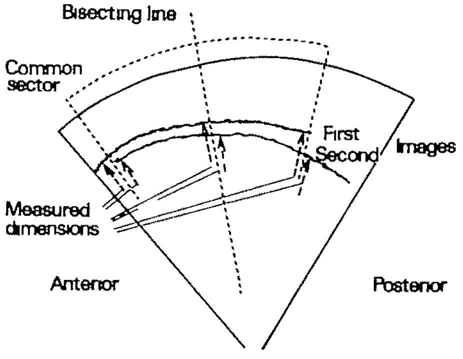

FIG. 2. Tracings of positions of the tongue surface and measured dimensions.

An increase in the radius was termed a cranial movement, and a reduction in the radius was termed a caudal movement. However, these are radial measurements and include a vector in the anterior–posterior dimension. As the centre of the field of view of the transducer was generally close to the cranio–caudal axis of the head, "caudal" movements of the anterior tongue include a posterior component, and "caudal" movements of the posterior segment include an anterior component.

RESULTS

In four patients it was not clear if apnoea was central or caused by airway obstruction and satisfactory data were obtained in 11 patients (table I). In the other patients, the ultrasound

TABLE I. *Details of patients studied*

Patient No.	Age (yr)	Height (cm)	Weight (kg)	Agent	Dose (mg)	Airway patency	Sector studied (degrees)
1	39	155	73	Thiopentone	375	Obstructed	57
2	22	160	59	Propofol	150	Obstructed	41
3	33	160	53	Thiopentone	250	Patent	63
4	32	157	76	Thiopentone	300	Obstructed	43
5	48	163	51	Propofol	100	Apnoea	72
6	55	165	62	Propofol	120	Patent	64
7	46	161	57	Propofol	80	Uncertain	60
8	39	178	73	Propofol	80	Uncertain	42
9	20	155	46	Thiopentone	100	Patent	65
10	28	150	57	Propofol	90	Uncertain	71
11	42	161	50	Thiopentone	200	Uncertain	76

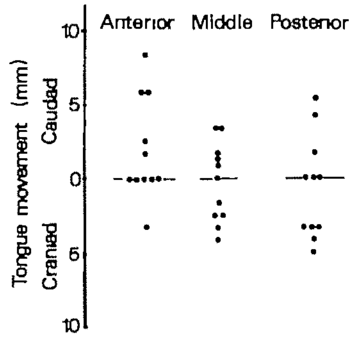

FIG. 3. Results: measurements of movement of the anterior, middle, and posterior portions of the tongue on induction of anaesthesia.

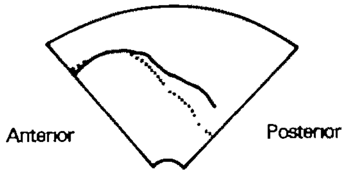

FIG. 4. Tracing of tongue position in expiration (——) and during inspiratory effort (....) in a patient with airway obstruction.

TABLE II. *Mean* (SD) *of tongue movements in patients given thiopentone* (n = 5) *and propofol* (n = 6)

	Anterior	Middle	Posterior
Thiopentone	0 (0)	−0.3 (1.4)	−0.8 (2.2)
Propofol	2.1 (2.5)	0.3 (1.6)	−0.2 (1.7)

images did not show an adequate degree of sector of the tongue. In general, the posterior part of the tongue was more difficult to image because of the acoustic shadow cast by the hyoid bone. The angle of sector analysed was more than 55° in eight of the 11 patients whose data are reported (mean in all 11 patients 59° (SD 12°)).

In the awake patients there was no movement of the tongue in relation to ventilation. On induction of anaesthesia, the movements observed (fig. 3) were small. The greatest movement was 8 mm caudad, which occurred in the anterior tongue. There was no consistent direction of movement. The probability of any movement of more than 8 mm lies between 0 and 28% (95% confidence limits, binomial distribution). In those patients in whom clinical signs of airway obstruction were identified, no consistent movement of the tongue occurred on induction of anaesthesia. In some patients, however, airway obstruction was associated with caudad movement of the posterior tongue towards the hypopharynx with each inspiratory effort (fig. 4). There was no consistent difference in the changes observed that could be attributed to the two induction agents used (table II).

DISCUSSION

Tongue position during anaesthesia has been investigated previously using radiography [1]. We have used ultrasound to image the tongue, principally to avoid the use of ionizing radiation. In addition, ultrasound may be used to construct a continuous, real-time image of the tongue over the period of induction. The ultrasound transducer was clamped below the chin to make gentle contact with the skin, so that the patient's head remained in a natural, relaxed position. However, it is possible that the transducer may have restrained jaw position to some extent, as muscle tone changed with loss of consciousness.

Ultrasound scanning produces a sagittal, cross-sectional image without the problem of overlapping structures produced on a lateral radiograph. The magnification and geometric distortion associated with conventional radiography are also avoided. There are, however, disadvantages in the use of ultrasound: ultrasound is reflected almost completely at an air–tissue interface, and so the position of the soft palate, epiglottis and posterior wall of the pharynx cannot be determined, and thus the dimensions of the airway itself cannot be judged. A dense acoustic shadow is cast by the hyoid bone, which in some patients limits imaging of the posterior tongue. Ultrasound scanning of the tongue has been used in a similar manner to evaluate tongue movement during speech [5] and swallowing [6].

The tongue image obtained was commonly in the form shown in figure 1, with a curvature convex in the cranial direction. The segment of the tongue observed was in the midline sagittal plane, but the direction of sight of the transducer was moved in this plane to obtain the best image. No attempt was made to measure the exact orientation of this direction, although generally it remained approximately parallel with the cranio–caudal axis of the head. Consequently, measurements were made of movements of the tongue surface towards or away from the transducer, and these do not imply an exact relationship to body axes. For example, it is clear from figure 1 that a caudad movement in the posterior tongue also reflects a movement anteriorly. The exact apportionment of these vectors is not possible. In addition, measurement was made only of the intersection of the tongue surface with the radius chosen; in the event of a change in tongue position, this intersection may not represent the same spot on the tongue surface. For these reasons, attempts to express tongue movement in exact anatomical directions were not considered realistic. The image considered was only of the midline sagittal section of the tongue. The tongue is curved also in the coronal plane, and a small reduction in this degree of curvature could cause apparent caudal movement of the image, with no true displacement of the mass of the entire tongue. Our observations depend, therefore, on the assumption that the overall shape of the tongue is not altered greatly.

Pressure from the transducer may have caused distortion and restriction of movement of the tongue. However, the influence of transducer pressure on tongue shape could be assessed easily by observing movement of the tongue as the transducer system was adjusted, and care was taken to minimize this influence.

Observed movement of the tongue during induction was small, the maximum being 8 mm caudad in the anterior part of the tongue in one patient. Maximum movement in the posterior tongue was 6 mm. These results compare with maximum movements of about 15–20 mm during swallowing observed with radiography [7] or ultrasound [Abernethy, unpublished data]. Overall, the results showed no consistent direction of movement. In two patients, caudad movement of the posterior tongue with each inspiratory effort was noted when airway obstruction was evident clinically. This observation would not be expected if airway obstruction were caused by posterior movement of the tongue, but is consistent with inspiratory effort against an airway which is occluded caudal to the tongue. Recent studies [3] using fibreoptic endoscopy have suggested that this is a common event. In normal subjects during natural sleep and in patients with sleep apnoea syndrome, airway obstruction can occur in some individuals at the soft palate, and in others in the hypopharynx [8, 9]. During anaesthesia, similar variation between individuals of the site of obstruction is likely.

Whilst our patients were awake, motion of the tongue in relation to ventilation was not observed. Some studies of tongue electrophysiology have shown phasic activity [10, 11], but in others the action in genioglossus was predominantly tonic [12, 13]. In addition, the use of premedicant or sedative drugs may reduce the activity of the tongue muscles [14]. However, it is possible that even if phasic muscle activity were present, this could act merely to maintain the position of the tongue against the changing pressure within the mouth.

Movement of the tongue in its posterior part would be most likely to cause obstruction of the pharynx. In our study, posterior movement of the posterior tongue would cause an increase in the distance measured along a radius from the centre of the image sector, and this would be expressed in our results as a cranially directed movement, although the direction has both cranial and posterior components. Such a movement occurred in only three patients and the greatest movement was 3.2 mm. The direct posterior component of this movement would be only a fraction of this, and is less than would be expected to cause obstruction on the basis of previous measurements. For example, in awake supine subjects, the distance from the posterior wall of the tongue to the posterior pharyngeal wall is about 10 mm (range 4.5–14 mm) [15].

In patients with sleep apnoea (in whom pharyngeal dimensions may be less than normal), the anteroposterior dimension of the pharynx posterior to the tongue is about 13 mm in the supine patient [16]. On induction of anaesthesia in elderly male subjects, posterior movement of the tongue of 6.4 mm was insufficient to cause contact with the posterior pharyngeal wall [17]. Consequently, we believe that the small, inconsistent changes in tongue position which we noted were unlikely to contribute significantly to airway obstruction after induction of anaesthesia.

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CARBOXYHAEMOGLOBIN CONCENTRATIONS, PULSE OXIMETRY AND ARTERIAL BLOOD-GAS TENSIONS DURING JET VENTILATION FOR Nd–YAG LASER BRONCHOSCOPY†

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SUMMARY

Oxygen saturation measured with pulse oximetry (Sp_{O_2}) is overestimated in the presence of carboxyhaemoglobin (COHb). Smoke produced during laser resection of tracheobronchial malignancies may increase concentrations of COHb. We have measured COHb concentrations in 14 patients undergoing laser resection and compared Sp_{O_2} with functional oxygen saturation (Sa_{O_2}) to ascertain if pulse oximetry is an accurate monitor of oxygen saturation. During the procedure frequent changes occur in ventilatory mechanics. Arterial blood-gas tensions were measured to see if gas exchange was satisfactory. Mean preoperative COHb was 1.4%. There was no significant change in COHb in any patient at any stage during treatment. The highest value was 2.05%. The mean difference between Sa_{O_2} and Sp_{O_2} was 1.13% (95% confidence interval 0.70–1.56%). Oxygen saturation may therefore safely be monitored by pulse oximetry in patients managed by our technique. Empirical setting of a jet ventilator provided acceptable blood-gas tensions, although sometimes it was necessary to increase the FI_{O_2} to > 0.3 to maintain oxygenation.

KEY WORDS

Complications. carboxyhaemoglobin. Monitoring. pulse oximetry. Surgery: tracheal, laser resection.

During the past decade, endoscopic laser therapy has become an established palliative treatment for patients with tracheobronchial malignancy. The thermal effects of the neodymium (Nd) YAG laser may be used to resect and cauterize intraluminal tumour from the large airways and, in appropriately selected patients, it is possible to palliate haemoptysis, breathlessness and other obstructive symptoms [1]. Patients with tumours obstructing the central airways appear to be particularly suitable for laser treatment. They are frequently close to asphyxiation at the time of referral and prompt restoration of an airway with the laser may provide a dramatic and sustained clinical improvement [2, 3].

Although treatment may be given under local or general anaesthesia, the techniques using general anaesthesia are thought to offer greater operative safety [4]. Maintaining adequate gas exchange during the initial stage of treatment may be difficult, especially in patients with impending asphyxia. This is complicated further by the need to maintain a low inspired oxygen concentration (FI_{O_2}) to reduce the risk of fire.

Pulse oximetry is a convenient method of monitoring arterial oxygenation during the procedure. The pulse oximeter determines arterial saturation by measuring the absorption of selected wavelengths of light passed through perfused tissues. However, only two wavelengths are used, 660 nm and 940 nm, and the oximeter distin-

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guishes only between deoxyhaemoglobin (Hb) and oxyhaemoglobin (HbO_2) [5, 6]. Smoke is produced during lasering and may result theoretically in increased concentrations of carboxyhaemoglobin (COHb). Because COHb absorbs almost identically to HbO_2 at 660 nm, saturation determined by pulse oximetry (Sp_{O_2}) is overestimated in the presence of COHb [7], and patients may be hypoxic even though the Sp_{O_2} is normal.

We assessed, therefore, the validity of pulse oximetry by measuring formation of COHb and comparing Sp_{O_2} with functional oxygen saturation (Sa_{O_2}) [8] measured directly from arterial blood samples obtained in patients undergoing treatment with a Nd–YAG laser.

PATIENTS AND METHODS

After Ethics Committee approval and written informed patient consent had been obtained, we studied 21 patients undergoing palliative laser resection of endobronchial tumours. Arterial blood-gas tensions and Sp_{O_2} were measured in all patients and in 14, COHb, methaemoglobin (MetHb), and Sa_{O_2} concentrations were measured also.

Premedication comprised i.m. atropine 0.6 mg 1 h before induction. On arrival of the patient in the bronchoscopy room, an electrocardiograph, non-invasive arterial pressure monitor and a pulse oximeter (Nellcor N100) were attached. The oximeter finger probe was placed on the index finger of the dominant hand and a cannula placed in the radial artery on the other side. After preoxygenation, anaesthesia was induced with i.v. etomidate 14–28 mg and alfentanil 1–2 mg i.v. Atracurium in bolus doses was administered to produce neuromuscular block as assessed by peripheral nerve stimulator. Anaesthesia was maintained with an infusion of propofol commenced immediately after induction. When relaxation was produced the rigid bronchscope was passed into the trachea and a jet ventilator (Accutronic VS 150s) attached to the side arm. The ventilator was adjusted to a rate of 60 b.p.m., an inspiratory time of 30% of each cycle and a driving pressure of 1.5–2.0 bar. Care was taken to observe good chest movement with ventilation. Shortly before lasering commenced, FI_{O_2} was reduced to 0.3. If the Sp_{O_2} decreased to less than 90% lasering was stopped and FI_{O_2} was increased until saturation was satisfactory. Arterial blood samples were taken at the following times: before induction, breathing air; before induction, breathing 100% oxygen; every 30 min thereafter during the procedure; 1–2 h after operation, breathing air. Corresponding Sp_{O_2} measurements were made with the exception of the postoperative values. Using a Radiometer OSM3 haemoximeter, COHb, Sa_{O_2}, and MetHb were measured twice on each blood sample and the mean of the two values noted.

All patients were treated with the 1.318-µm output beam of a specially designed continuous wave Nd–YAG laser (Medilas 2; MBB-Medizintechnic). Treatments were given under general anaesthesia using a combination of flexible and rigid bronchoscopes. After induction of anaesthesia, the trachea was intubated with a rigid Shapshay laser bronchoscope (Storz; Model 10317 LA) and the lungs jet-ventilated with an oxygen–air mixture. A fibreoptic bronchoscope with a 2.6-mm diameter biopsy channel (Pentax FB-19H) was passed inside the lumen of the rigid instrument and the optical fibre which transmits the laser beam was passed down the channel of the flexible bronchoscope. Laser irradiation was given at powers ranging from 10 to 20 W in pulses of up to 1 s. At the end of treatment, coagulated tumour debris was removed with flexible and rigid biopsy forceps.

The total energy (J) delivered by the laser was recorded for each patient and the operator graded the amount of smoke produced on a three-point scale: large, moderate and small.

The Sp_{O_2} and Sa_{O_2} values were recorded and presented graphically by the method described by Bland and Altman [9] (fig. 2). A paired *t* test was used to compare preoperative COHb with the greatest value recorded subsequently for each patient.

RESULTS

COHb values were measured in 14 patients (10 male). All had a history of smoking, but none had

TABLE I. *Patient data (mean (range)) for the 14 subjects in whom HbCO was measured*

Age (yr)	Duration of anaesthetic (min)	Amount of smoke	Laser energy (J)
60.9 (43–71)	108 (47–153)	Small = 4 Moderate = 8 Large = 2	7145 (3093–14785)

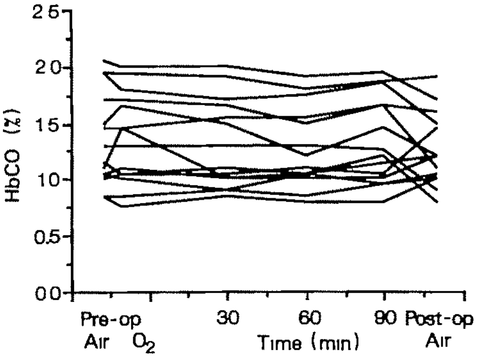

FIG. 1. Percentage carboxyhaemoglobin (HbCO) for individual patients. Results are preoperative, breathing air; preoperative, breathing 100% oxygen; at 30, 60 and 90 min after induction; postoperative, breathing air.

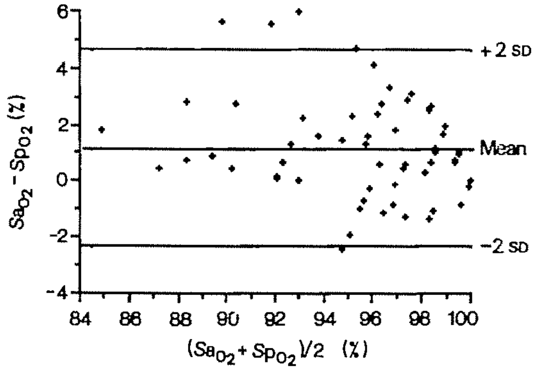

FIG. 2. Difference between functional oxygen saturation (Sa_{O_2}) and saturation determined by pulse oximetry (Sp_{O_2}) at average values of saturation measured by both methods (mean, 2 SD).

smoked within 10 days of the procedure. Patient data are shown in table I. Mean preoperative COHb was 1.4%. There was no consistent or important change in any patient at any stage during treatment (fig. 1). The greatest value was 2.05%—a preoperative value.

In five volunteers who were habitual smokers mean COHb concentrations were 6.2% before and 7.2% immediately after one cigarette. In patients, the mean difference between Sa_{O_2} and Sp_{O_2} was 1.13% (fig. 2) with a 95% confidence interval of 0.70–1.56%.

In addition to these 14 patients, measurements of arterial blood-gas tensions were made in a further seven. In one patient, the arterial cannula was placed after induction and pre-induction values were not available. In the other 20 patients before induction, mean Pa_{O_2} was 10.6 kPa breathing air with three subjects having a $Pa_{O_2} < 8$ kPa. Of the 68 arterial blood-gas measurements during anaesthesia, 11 were of $Pa_{O_2} < 8$ kPa, two with $Sp_{O_2} < 90\%$. MetHb concentrations averaged 0.5% (range 0.2–0.9%) (table II). Postoperative Pa_{O_2} breathing room air was < 8 kPa in three patients. In one, the preoperative value was unknown; in another it was 9.5 kPa, and in the third the preoperative value was similar—7.1 kPa, compared with 7.2 kPa after operation. This last patient developed airway obstruction soon after tracheal extubation, with a Pa_{CO_2} of 7.8 kPa. A bronchoscope was re-inserted and secretions were removed. After a short period of ventilation and treatment with bronchodilators, blood-gas values improved. There were no other postoperative respiratory problems. Mean Pa_{CO_2} before operation was 4.9 kPa (range 3.1–5.7 kPa) and, of the readings during anaesthesia, the minimum value was 2.6 kPa and the maximum 8.8 kPa. After operation, with the exception of the patient who required ventilation, the smallest value was 3.5 kPa and the greatest 5.5 kPa.

DISCUSSION

The effect of abnormal haemoglobins on Sp_{O_2} depends on how their light absorption compares with that of Hb and HbO_2 at 660 nm and 940 nm [5]. COHb absorbs almost identically to HbO_2 at

TABLE II. *Arterial blood-gas values (mean (SEM))*

	Before op.					After op.
	Air	100% O_2	+30 min	+60 min	+90 min	Air
n	20	19	21	20	17	21
Pa_{O_2} (kPa)	10.53	36.21	12.46	12.82	10.09	10.23
	(0.48)	(3.04)	(1.23)	(1.37)	(0.62)	(0.49)
Pa_{CO_2} (kPa)	4.89	5.08	4.95	4.93	4.56	5.17
	(0 12)	(0.18)	(0.34)	(0.39)	(0.36)	(0.19)

660 nm and the pulse oximeter responds almost as if it were HbO_2. Various formulae have been calculated to account for the COHb, but fractional Sa_{O_2} [8] approximates to ($Sp_{O_2} - 0.9\ Sa_{CO}$) [7, 10] where Sa_{CO} is the percentage of COHb. Therefore, in patients with increased COHb the pulse oximeter overestimates oxygen saturation of blood. Furthermore, the oxyhaemoglobin dissociation curve is shifted to the left [11] in the presence of COHb, thus decreasing oxygen delivery to the tissues. Methaemoglobin (MetHb) may also have an effect [12], but this was not present in significant amounts in our patients.

The OSM3 haemoximeter measures the absorption by haemoglobin of light at six different wavelengths and can determine accurately the concentrations of Hb, HbO_2, MetHb and COHb. The *functional* Sa_{O_2} is then calculated: $HbO_2/(HbO_2 + Hb)$. The *fractional* Sa_{O_2} is $HbO_2/(HbO_2 + Hb + COHb + MetHb)$ and therefore takes account of the presence of abnormal haemoglobins; for our patients this was approximately 0.98 of the functional Sa_{O_2}.

Smoke is generated by laser resection of tumours in the upper airway. It may obscure the operator's view of the airway to an extent that has prompted the design of a special ventilator to remove the smoke [13]. It has also been suggested previously that laser therapy may result in increased concentrations of COHb [14]. If this were to occur in patients whose oxygen saturation was monitored by pulse oximetry, they might be hypoxic even though Sp_{O_2} records normal values. It is possible that different types of laser may result in different degrees of smoke generation; it is not possible, therefore, to extrapolate our data to all patients who receive laser bronchoscopy. However, our results are in agreement with those of Brutinel, McDougall and Cortese [14], who found no change in COHb in patients who received therapy with a Molectron Nd-YAG laser operating at a wavelength of 1.064 μm.

Several anaesthetic techniques of ventilation have been developed for this procedure [15–22]. We used a total i.v. anaesthetic and mechanical ventilation through the side arm of a Storz rigid bronchoscope. The mechanics of ventilation change frequently during the procedure. The passage of the fibreoptic scope through the rigid scope alters the compliance and resistance of the system and blood, secretions and debris also interfere with ventilation. The distribution within the airways and alveolae of any carbon monoxide produced depends largely on the pattern of ventilation. Although ventilator settings were constant, because of the factors listed above, ventilation was variable and could not be standardized. It cannot be assumed that other ventilation techniques will produce the same results, but we have no reason to suspect that an alternative method providing good gas exchange and subject to the same sources of variability would result in substantially greater concentrations of COHb.

Oxygenation was adequate and was monitored satisfactorily by pulse oximetry. Pa_{CO_2} was generally within acceptable values when good chest movement was observed. Although our patients had compromised airways, in all but one, postoperative arterial blood-gas values comparable to preoperative values were achieved breathing air (FI_{O_2} 0.21) within 1–2 h. There was no evidence that the procedure caused short-term respiratory embarrassment in the postoperative period.

This study has shown that treatment with a Nd–YAG laser operating at a wavelength of 1.318 μm did not produce clinically significant concentrations of COHb with the anaesthetic and ventilation techniques used. Pulse oximetry may therefore be used reliably and accurately to monitor oxygen saturation during treatment. Empirical settings of a jet ventilator provided acceptable blood-gas values, despite changes in ventilatory mechanics, although sometimes it may be necessary to increase FI_{O_2} to > 0.3 to maintain oxygenation.

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EFFECTS OF ENFLURANE AND ISOFLURANE IN AIR–OXYGEN ON CHANGES IN THERMAL BALANCE DURING AND AFTER SURGERY

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SUMMARY

The temperatures in the aural canal (core), skeletal muscle and skin surface were measured during anaesthesia and surgery in 32 healthy females undergoing total abdominal hysterectomy and for 4 h after operation. The patients were allocated randomly to one of four groups according to the end-tidal concentration of volatile anaesthetic: 1 MAC isoflurane, 1 MAC enflurane, 1.8 MAC isoflurane and 1.8 MAC enflurane. The lungs were ventilated with an air–oxygen mixture. Neuromuscular block was produced with pancuronium. Room temperature and i.v. fluid administration were standardized. Aural canal, muscle and mean skin temperatures decreased significantly in all groups during surgery ($P < 0.001$). The decrease in core and muscle temperatures, and mean body heat was significantly greater in the 1.8 MAC groups than in the 1 MAC groups for both volatile agents ($P < 0.001$). However, there was a significantly greater decrease in core temperature and mean body heat in the isoflurane compared with the enflurane group ($P < 0.026$). Body temperature returned to preoperative values during the recovery period. There was a significantly greater rate of rewarming during the first 1 h of recovery in the 1.8 MAC groups compared with the 1 MAC equivalent ($P < 0.001$), and this was independent of the volatile agent used. The present results are compared with those reported previously in which nitrous oxide was added to the volatile agents. The decrease in body temperature depends upon the concentration of vapour used. However, it appears that isoflurane, without nitrous oxide, caused greater loss of body heat than enflurane.

KEY WORDS

Anaesthetics, volatile: enflurane, isoflurane Temperature thermoregulation.

Anaesthesia and surgery are associated commonly with a decrease in body temperature [1] which returns towards normal in the postoperative period. In a recent study, Ramachandra and colleagues [2] investigated the effect on body temperature of different concentrations of three volatile anaesthetic agents: halothane, enflurane and isoflurane, given with 70% nitrous oxide in oxygen. They demonstrated that the loss of body heat during surgery was related to the concentration and not the volatile agent used. Because of the design of their study they were unable to make quantitative comparisons between agents.

The effects of administration of nitrous oxide on various organs have been reviewed [3]. Because of its sympathetic stimulating action, nitrous oxide may antagonize, to some extent, the depressant cardiovascular effects caused by most volatile agents used in clinical practice [4].

We are not aware of any detailed study on thermoregulation during anaesthesia and surgery when volatile agents are administered in an air–oxygen mixture. The aim of this study was, therefore, to compare the effects of different fractions of minimum alveolar concentration (MAC) of isoflurane and enflurane administered

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without nitrous oxide on body temperature during and after surgery.

PATIENTS AND METHODS

Approval for the study was obtained from the Hospital Ethics Committee. We studied 32 patients, undergoing elective total abdominal hysterectomy for menorrhagia, after informed consent was obtained. All patients were otherwise healthy.

Using a random number generated by a computer program designed by Wichmann and Hill [5], each patient was allocated to one of four groups of eight patients, to receive an end-tidal concentration (mean (SD)) of 1 MAC isoflurane (1.13 (0.04)%), 1 MAC enflurane (1.67 (0.03)%), 1.8 MAC isoflurane (2.03 (0.04)%) or 1.8 MAC enflurane (2.98 (0.04)%). The decision to limit both enflurane and isoflurane concentrations to 1.8 MAC was dictated by the high incidence of profound hypotension and ventricular arrhythmias observed in a preliminary study with higher doses. A similar incidence of cardiovascular disorders was reported previously in human volunteers receiving 2 MAC enflurane without nitrous oxide [6].

Premedication comprised i.m. papaveretum and hyoscine 1 h before operation. Anaesthesia was induced with thiopentone and tracheal intubation facilitated with pancuronium. The lungs were ventilated to normocapnia with a mixture of oxygen enriched air. The concentration of oxygen was monitored with a fuel cell oximeter and maintained at 35%. Anaesthesia was maintained with the agent and concentration determined by the randomization process.

The end-tidal concentration of anaesthetic was measured continuously during the study using an anaesthetic gas analyser (Engstrom, Emma); calibration was checked in each experiment against volumetrically prepared standards.

After the skin was cleansed with chlorhexidine solution, patients were draped in the standard manner with sterile cotton drapes and only the head and operative site were exposed. No active warming or heat conservation measures were taken. Hartmann's solution was administered i.v., at room temperature, at a rate of 6 $\text{ml kg}^{-1}\,\text{h}^{-1}$ during the period of study. Mean theatre temperature and relative humidity were 22.0 °C (range 20–24 °C) and 52% (34–68%), respectively during the study.

At the end of surgery, all patients were covered in a cotton sheet, blanket and bedspread and transferred to the recovery area where they remained for the first 4 h after operation. Analgesia was provided as required with papaveretum i.m. Ambient temperature in the recovery room was maintained at 22.0–26.0 °C.

At induction of anaesthesia, a thermocouple probe was inserted in the aural canal and secured with cotton wool to exclude draughts. Aural canal temperature was measured as an indicator of core temperature. Skin temperature was taken from four predetermined sites which were marked: upper arm, nipple, mid thigh and calf. A sterile needle muscle temperature probe was inserted into the lateral portion of the quadriceps femoris muscle to a depth of 4–5 cm from the skin surface and approximately 15–20 cm above the knee. This probe was left *in situ* during the surgery and removed at the end of anaesthesia.

The temperature probes and the thermometer used (Comark Electronics) were calibrated against a National Physics Laboratory mercury in glass thermometer and found to be accurate to 0.05 °C.

Aural canal and skin temperatures were measured before and at the end of surgery, and every 1 h for the first 4 h after operation. Muscle temperature was recorded before and at the end of the operation. Mean skin temperature (MST) was calculated using the formula proposed by Ramanathan [7]:

$$\text{MST }(^\circ\text{C}) = 0.3\,(\text{nipple temp.} + \text{arm temp.}) + 0.2\,(\text{thigh temp.} + \text{calf temp.})$$

Mean body temperature (MBT) was calculated from an equation proposed by Colin and colleagues [8]:

$$\text{MBT }(^\circ\text{C}) = 0.66 \times \text{aural canal temp.} + 0.34 \times \text{MST}$$

Mean body heat (MBH) (kJ) was calculated from MBT and corrected for body weight [9]:

$$\text{MBH (kJ)} = \text{MBT} \times \text{body weight} \times 0.83\ (\text{specific heat}) \times 4.186$$

Statistical analysis

Analysis of variance was performed for each of the body temperature measurements to compare the type and concentration of anaesthetic agent, the time of measurement of body temperatures and their interactions. Comparisons of time of measurement were made within subjects, whilst those of type and concentration of anaesthetic agent only were made between subjects. For analysis of aural canal temperature, mean skin temperature and mean body heat, the time of measurement was subdivided into non-orthogonal contrasts, estimating the changes in temperature during surgery and trends in temperature after surgery. The normality of residuals and the equality of residual variances were tested using Shapiro–Wilks' W test [10] and Schweder's test [11], respectively.

RESULTS

The four groups were comparable in respect of patient and clinical data (table I). Tachycardia and, occasionally, hypotension were observed after administration of 1.8 MAC enflurane. No major haemodynamic changes were reported with isoflurane. No blood products were required during the study. During the recovery period studied, all patients received one dose of papaveretum 15 mg i.m.

Changes in temperature during surgery

There were significant changes in temperature and MBH during surgery ($P < 0.001$) (tables II–V). These changes were found to be significantly different ($P < 0.001$) between the concentrations of anaesthetic agents for aural canal temperature, MBH and muscle temperature. The decreases in temperature during surgery were greatest in patients receiving 1.8 MAC of anaesthetic agent, for each of these three variables (table VI). The decreases in temperature during surgery were found also to be significantly different ($P = 0.027$ and $P = 0.026$) between the types of anaesthetics for aural canal temperature and MBH, respectively. In both variables the decrease in temperature was greatest for isoflurane (table IV).

There were no significant interactions between the type of anaesthetic agent, concentration and time.

Rewarming after surgery

Rewarming after surgery was analysed only for mean skin and aural canal temperatures, and MBH.

The temperatures at 1-h intervals after surgery were significantly different ($P < 0.001$). There were significant linear and quadratic trends in temperature in each of the variables ($P < 0.001$), showing that initially the temperature increased rapidly, followed by a slowing down of the rate of the increase.

The pattern of increasing body temperature after surgery differed significantly between concentrations of the anaesthetic agents, but did not differ significantly between type of anaesthetic

TABLE I. *Patient characteristics and clinical data (mean (range))*

	1 MAC Isoflurane ($n = 8$)	1 MAC Enflurane ($n = 8$)	1.8 MAC Isoflurane ($n = 8$)	1.8 MAC Enflurane ($n = 8$)
Age (yr)	41 (33–48)	39 (27–49)	43 (35–51)	42 (29–53)
Body weight (kg)	64 (48–76)	66 (58–75)	64 (50–79)	68 (52–88)
Body mass index (kg m^{-2})	24.9 (20.5–29.5)	24.3 (21.3–30.0)	24.2 (17.6–31.6)	25.9 (19.3–31.3)
Preoperative fasting time (h)	10 (5–13)	10 (4–14)	12 (8–15)	12 (9–15)
Blood loss (ml)	223 (150–330)	297 (150–640)	281 (150–550)	231 (150–310)
Duration of surgery (min)	62 (30–85)	68 (35–90)	61 (45–88)	74 (50–95)

TABLE II. *Average (SEM 0.15) aural canal temperatures (°C) before and at 1-h intervals after surgery*

	Before surgery	End of surgery	Time after surgery (h)			
			1	2	3	4
1 MAC Isoflurane	35.9	34.9	35.6	35.9	36.3	36.5
1 MAC Enflurane	36.1	35.6	35.9	36.3	36.6	36.8
1.8 MAC Isoflurane	36.2	34.4	35.5	36.0	36.2	36.5
1.8 MAC Enflurane	36.6	35.0	36.0	36.4	36.9	37.1

TABLE III. *Average* (SEM *0.26*) *mean skin temperature* (°*C*) *before and at 1-h intervals after surgery*

	Before surgery	End of surgery	Time after surgery (h) 1	2	3	4
1 MAC Isoflurane	32.6	31.3	32.8	33.7	33.8	34.3
1 MAC Enflurane	32.6	31.9	33.1	34 1	34.4	34 7
1.8 MAC Isoflurane	32.5	31.4	33 1	33.5	33.9	34.2
1.8 MAC Enflurane	32.7	32.0	32.7	33.5	34.1	34.5

TABLE IV. *Average* (SEM *425*) *mean body heat* (*kJ*) *before and at 1-h intervals after surgery*

	Before surgery	End of surgery	Time after surgery (h) 1	2	3	4
1 MAC Isoflurane	7732	7478	7687	7802	7862	7940
1 MAC Enflurane	7936	7803	7956	8087	8158	8205
1.8 MAC Isoflurane	7741	7395	7681	7775	7834	7916
1.8 MAC Enflurane	8287	7980	8195	8315	8437	8507

TABLE V. *Average* (SEM *0 22*) *muscle temperature* (°*C*) *before and after surgery*

	Before surgery	After surgery
1 MAC Isoflurane	35.9	35.1
1 MAC Enflurane	35.5	34.7
1.8 MAC Isoflurane	35.7	34.4
1.8 MAC Enflurane	36.1	34.8

agent for aural canal temperature and MBH. For aural canal temperature there was a significant difference between concentrations of anaesthetics for linear trend ($P < 0.001$) and quadratic trend ($P = 0.022$). During the first 1 h after surgery, aural canal temperature at 1.8 MAC increased to reach the same temperature as for 1 MAC (fig. 1). For MBH, the linear trend was significantly different between concentrations ($P = 0.017$). MBH was consistently greater at 1.8 MAC than at 1 MAC, and the rate of temperature increase was greater at 1.8 MAC (fig. 2).

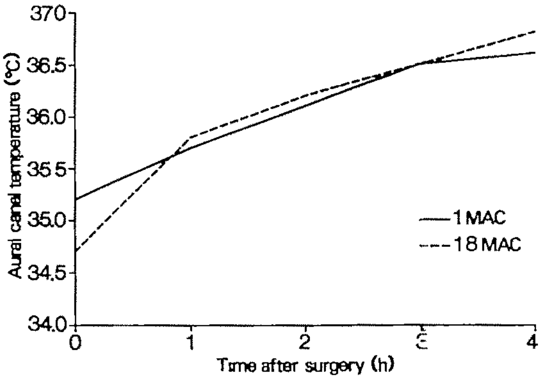

FIG. 1. Change in aural canal temperature after surgery averaged over volatile agents for each MAC value.

TABLE VI. *Decrease in temperature during surgery by type and concentration of anaesthetic. Iso.* = *Isoflurane*; *Enf.* = *enflurane*

	Concentration 1 MAC	1.8 MAC	Anaesthetic agent Iso.	Enf.	SEM of mean decrease
Aural canal temp. (°C)	0.8	1.7	1.4	1.1	0.12
Mean skin temp. (°C)	1.0	0.9	1 2	0 7	0.19
Muscle temp. (°C)	0.8	1.3	1.0	1.0	0.10
Mean body heat (kJ)	193	327	301	220	25

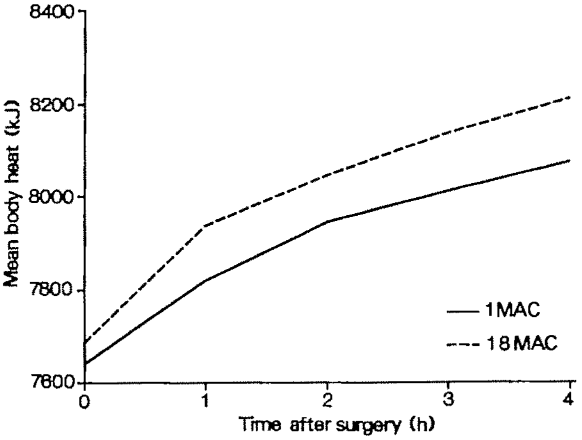

FIG. 2. Changes in mean body heat after surgery averaged over volatile agents for each MAC value.

DISCUSSION

The present study showed that aural canal, mean skin and muscle temperatures decreased during surgery when either enflurane or isoflurane anaesthesia was administered without nitrous oxide. The reduction in aural canal and muscle temperatures in the 1.8 MAC groups was significantly greater than that occurring in the 1 MAC groups, independent of the anaesthetic agent used. However, when the effect of the two vapours was analysed, isoflurane caused a significantly greater reduction in core temperature during surgery than enflurane.

Anaesthetic agents contribute to negative thermal balance by interfering with normal thermoregulatory mechanisms at several sites, both central and peripheral [12]. The thermoregulatory response is thought to be dependent on the concentration and not the anaesthetic agent, as shown recently by Ramachandra and colleagues [2]. The results of the present investigation agreed with those of Ramachandra's group in demonstrating a relationship between concentrations of two volatile agents and intraoperative loss of heat. However, while both isoflurane and enflurane exhibited similar effects on core temperature (a decrease of 0.6 °C, at low concentration, during surgery) in their study, in the present investigation isoflurane in an air–oxygen mixture caused a significantly greater reduction in aural canal temperature and heat balance.

Several explanations for these results may be proposed. The nitrous oxide supplementation in the study of Ramachandra and colleagues could have affected thermoregulation. This might have been caused by the sympathomimetic effect of nitrous oxide in the presence of volatile agents; this would be expected to obtund the reduction in body temperature by antagonizing the vasodilatation produced, particularly by isoflurane. A twofold increase in skin blood flow during administration of either 1 or 2 MAC isoflurane in an air–oxygen mixture compared with the same MAC values in the presence of nitrous oxide in oxygen has been reported previously [13]. In contrast, Smith and colleagues [14] were unable to report similar differences in skin blood flow when nitrous oxide was added to enflurane. These authors concluded that nitrous oxide does not stimulate the cardiovascular system in the presence of enflurane as it does when added to other inhalation agents such as halothane [15], ether [16] or fluroxene [17].

Difference in the actions of isoflurane and enflurane could account for their different thermoregulatory effects during operation. Radiant heat loss, which is controlled by vasodilatation, accounts for the major part of intraoperative heat loss. Isoflurane, which has a greater vasodilator action than enflurane, would be expected to cause greater intraoperative reduction in temperature [18]. While thermoregulatory vasoconstriction might have occurred at low MAC of enflurane [19], a critical level of thermoregulatory depression was perhaps exceeded with greater concentrations.

Skeletal muscle temperature was measured during anaesthesia and surgery in order to evaluate the effect of two concentrations of two different volatile agents on muscle thermogenesis. It is interesting to note that, on average, the temperature recorded in the quadriceps femoris muscle was 0.3 °C less than the aural canal temperature. While muscle is thought conventionally to represent a site at which energy-requiring processes occur, and therefore releasing heat, it is not clear if the smaller values observed in this study might be a result of the effect of neuromuscular blockers on muscle tone or reduced vascular perfusion [20].

In the present investigation, the changes in muscle temperature observed during anaesthesia and surgery were related to the concentration and not the anaesthetic agent used. Isoflurane is known to cause a greater, dose dependent, increase in muscle blood flow than enflurane. However, the effects of isoflurane on muscle temperature were not evident in the present investigation. It appears, therefore, that measurement of muscle temperature, as an indicator of muscle blood flow during anaesthesia, must be interpreted with caution.

Body temperature in all groups returned to preoperative values after surgery. There was a significantly greater rate of rewarming in the 1.8 MAC groups compared with the 1 MAC equivalents occurring during the first 1 h of recovery as shown by the changes in aural canal temperature and MBH. With time, core temperature in the four groups approached preoperative values. The rate of change in mean skin temperature during recovery was similar for all groups, with the greatest increase during the first 1 h after operation. These results are in agreement with those of Ramachandra and colleagues [2], who were unable to show any significant difference between these inhalation agents during the rewarming period.

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PHARMACOKINETIC INTERACTION OF PROPOFOL AND FENTANYL: SINGLE BOLUS INJECTION STUDY

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SUMMARY

The effect of pretreatment with fentanyl on the pharmacokinetics of a single bolus of propofol was studied in 17 female patients (mean age 35 yr), ASA grade I. Eight patients received fentanyl 1.5 μg kg^{-1} 5 min before induction of anaesthesia. In all patients anaesthesia was induced with propofol 2.5 mg kg^{-1} and maintained with halothane and nitrous oxide in oxygen. Pretreatment with fentanyl resulted in prolonged apnoea in all eight patients compared with three of nine patients in the control group. The pharmacokinetic values for propofol were described by a three-compartment mammillary model with rapid distribution phases ($T_{\frac{1}{2}}^{\alpha}$ mean (SEM) 3.1 (2.0) min and $T_{\frac{1}{2}}^{\beta}$ 44 (9.1) min) and a slower final phase of $T_{\frac{1}{2}}^{\gamma}$ 520 (96) min. The clearance of propofol was rapid (mean 1.6 (0.24) litre min^{-1}). Propofol was distributed initially into a relatively large central compartment (mean 23.7 (6.6) litre) and was extensively redistributed (mean V^{ss} 593 (157) litre). There was no difference in the pharmacokinetic profile of propofol between the two groups.

KEY WORDS

Anaesthetics, intravenous: propofol Analgesics· fentanyl Pharmacokinetics

Propofol is a short acting i.v. anaesthetic agent which may be given as a single bolus or as a continuous infusion. Prys-Roberts [1] has shown previously that patients who received fentanyl 5 μg kg^{-1} as a bolus at the time of induction with the Cremophor formulation of propofol 1.5 mg kg^{-1} followed by an infusion of propofol 3 mg kg^{-1} h^{-1} took significantly longer to open the eyes and had significantly greater blood concentrations of propofol than patients who were not pretreated with fentanyl. Cockshott and co-workers [2] conducted a similar study using the emulsion formulation of propofol 2.5 mg kg^{-1} as a single bolus. They showed that, throughout the sampling period, the mean blood concentrations of propofol were 50% greater in those who were pretreated with fentanyl 100 μg. That fentanyl 100 μg may have such a marked effect on the pharmacokinetics of propofol was thought worthy of further investigation.

PATIENTS AND METHODS

Seventeen unpremedicated female patients, ASA grade I, who presented for minor elective gynaecological procedures were studied following Ethics Committee approval and informed consent. All patients were aged between 18 and 50 yr and weighed not more than 120% of ideal body weight. Patients were excluded if they had hepatic, renal, haematological, metabolic or cardiovascular disease or if they were receiving any medication.

A 16-gauge cannula was inserted into a vein in the antecubital fossa under local anaesthesia for blood sampling and was flushed regularly with heparinized saline. The patients were allocated randomly to group C (control) or group F. Fentanyl 1.5 μg kg^{-1} was administered to patients in group F, 5 min before induction of anaesthesia. Anaesthesia was induced in all patients with i.v. propofol 2.5 mg kg^{-1} injected via a separate cannula in the contralateral forearm over a period of 20 s. Anaesthesia was maintained with 1–2% halothane and 66% nitrous oxide in oxygen via a Bain circuit with spontaneous ventilation.

Heart rate and arterial pressure were measured using an automatic non-invasive device (Dina-

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map), before and every 1 min during surgery. Induction time was measured from the start of injection of propofol to loss of verbal contact. Apnoea lasting for greater than 60 s was considered significant. At the end of surgery, both nitrous oxide and halothane were discontinued simultaneously and the patients breathed 100 % oxygen. Recovery times were measured from the time that nitrous oxide and halothane were discontinued to eye opening and recalling the correct date of birth.

Blood samples (5 ml) were taken for measurement of blood concentrations of propofol at baseline and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480, 720 and 1320 min after the end of administration of propofol. The samples were mixed in tubes containing potassium oxalate, and stored at 4 °C whilst awaiting analysis. Propofol concentrations in the blood samples were determined by a modification of the method described by Cockshott and colleagues [2]. The cyclohexane:hexane (3:1) extract was basified with tetramethyl ammonium hydroxide and evaporated to dryness under nitrogen. After reconstitution, the residue was subjected to high pressure liquid chromatography with fluorescence detection. This method has a limit of measurement of approximately 2 ng ml^{-1} and the inter-batch coefficient of variation of the assay over the concentration range observed in this study was approximately 8 %.

Pharmacokinetic analysis of each data set was performed using the extended least squares curve fitting program ELSFIT [3]. This program estimates individual weighting for each data point under the variance model to achieve maximum likelihood for the data. The data were fitted into a two- and then a three-compartment model and information criteria (Akaike) were used to compare maximum likelihood for each model. The areas under the time–concentration curve $AUC_{0-\infty}$ and AUC_{0-1320} were determined using the trapezoidal approximation for each individual patient. The pharmacokinetic data were derived separately for each individual data set.

The total body clearance (Cl) was calculated as

$$Cl = \text{dose} \times \text{AUC}^{-1}$$

and the volume of distribution at steady state (V^{ss}) was calculated as

$$V^{ss} = \text{dose} \times \text{AUMC} \times \text{AUC}^{-2}$$

where

$$\text{AUMC} = (A \times \alpha^{-2}) + (B \times \beta^{-2}) + (C \times \gamma^{-2})$$

The demographic data and derived pharmacokinetic parameters were analysed using Student's t test, propofol concentrations using the repeated measures MANOVA and the Kruskal–Wallis test was used to compare recovery times. The incidence of complications was compared using chi-square test. The minimum level of statistical significance was taken as $P < 0.05$.

RESULTS

There were no significant differences between the two groups with respect to age or weight (table I). Anaesthesia was induced successfully in all patients. Excitatory phenomena and involuntary movements were not seen. Mild pain on injection was experienced by two patients in the fentanyl group and none in the control group. Apnoea occurred in all eight patients in the fentanyl group (median 210 (range 60–420) s) and in three of nine patients in the control group (120 (90–300) s) ($P < 0.01$). These patients' lungs were ventilated manually with 1 % halothane and 66 % nitrous oxide in oxygen via a Bain circuit. No postoperative complications occurred in any of the patients during the 24-h period. There was no difference in the duration of anaesthesia and recovery times between the groups (table II). All patients demonstrated secondary peaks in whole blood concentrations of propofol associated with awakening. The propofol concentration (median

TABLE I. *Patient data (mean (SD))*

	Control group	Fentanyl group
Age (yr)	36.3 (7.2)	33.1 (8.0)
Weight (kg)	59.2 (10.7)	62.3 (9.5)

TABLE II. *Median (range) duration of anaesthesia and recovery times*

	Control group	Fentanyl group
Anaesthetic duration (min)	19.5 (15–33)	20.0 (14–42)
Eyes opening (min)	6.0 (2–11)	4.5 (3–8)
Correct date of birth (min)	7.0 (3–11)	6.0 (4–11)

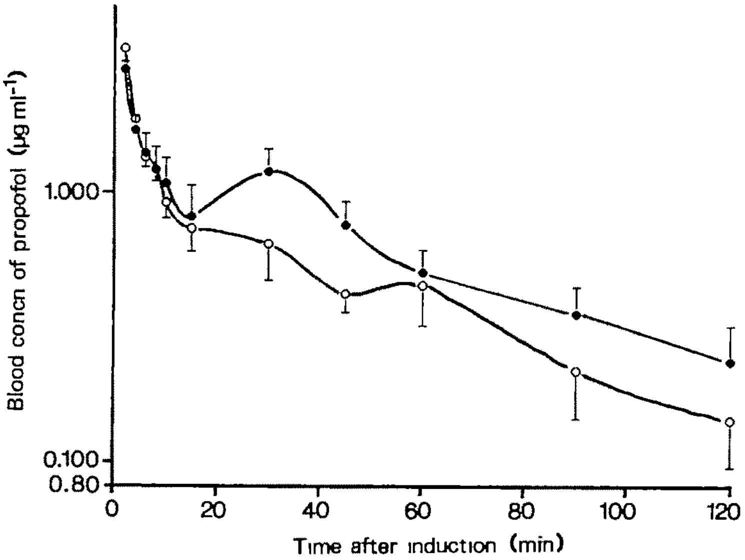

FIG. 1. Mean (SEM) blood concentrations of propofol plotted on a logarithmic scale up to 120 min after induction with propofol 2.5 mg kg^{-1} for the fentanyl (○) and the control (●) groups.

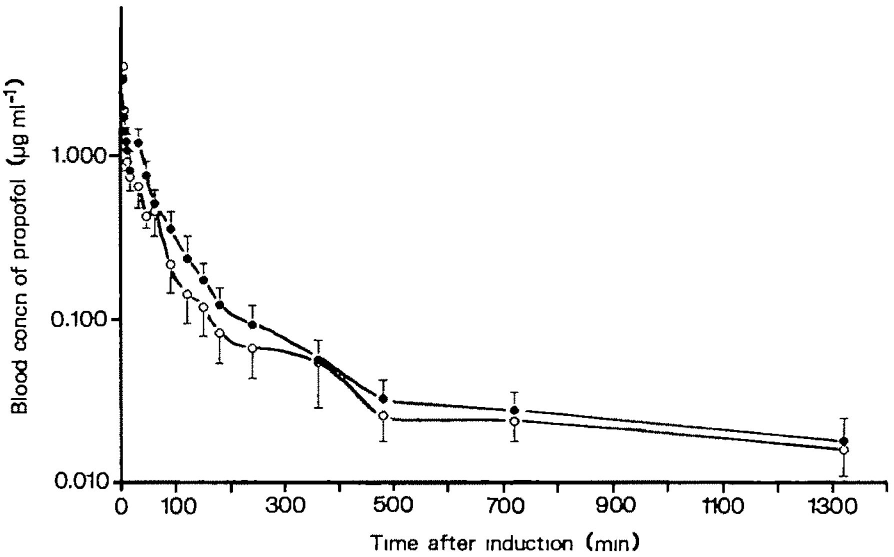

FIG. 2. Mean (SEM) blood concentrations of propofol plotted on a logarithmic scale up to 22 h (1320 min) after induction with propofol 2.5 mg kg^{-1} for the fentanyl (○) and control (●) groups.

(range)) at awakening was 0.7 (0.2–1.7) μg ml^{-1} in the fentanyl group and 0.8 (0.2–3.0) μg ml^{-1} in the control group. These did not differ significantly.

The mean propofol concentration profiles for the two treatment groups for time points up to 120 min and 22 h (1320 min) are shown in figures

TABLE III. *Mean* (SEM) *propofol pharmacokinetic data*

	Control group ($n = 9$)	Fentanyl group ($n = 8$)
A (μg ml^{-1})	8.75 (1.76)	7.40 (1.19)
α (min^{-1})	1.53 (0 90)	0 70 (0 18)
B (μg ml^{-1})	0.76 (0.17)	1.12 (0.17)
β (min^{-1})	0.021 (0 004)	0 025 (0.005)
C (μg ml^{-1})	0.083 (0.022)	0.047 (0.014)
γ (min^{-1})	0.002 (0.001)	0 0016 (0.001)
$T_{\frac{1}{2}}^{\alpha}$ (min)	3.1 (2.03)	1.5 (0.362)
$T_{\frac{1}{2}}^{\beta}$ (min)	43 5 (9 1)	34.0 (4.9)
$T_{\frac{1}{2}}^{\gamma}$ (min)	520 (96)	650 (212)
AUC$_{0-\infty}$ (μg min ml^{-1})	145.0 (37.3)	103.8 (27 6)
AUC$_{0-1320}$ (μg min ml^{-1})	139 3 (35.3)	100 0 (26 2)
V_1 (litre)	23.7 (6.6)	22.8 (5.0)
V^{ss} (litre)	593 (157)	996 (435)
Total body clearance		
(litre min^{-1})	1.61 (0.24)	1.89 (0.26)
(ml min^{-1} kg^{-1})	26.8 (3.8)	30 0 (3.3)

1 and 2, respectively. The mean AUC$_{0-\infty}$ value for the fentanyl group (104 μg min ml^{-1}) was not significantly different from the values of the control group (137 μg min ml^{-1}). The mean AUC$_{0-1320}$ also revealed no difference between the groups.

The data were treated as conforming to a three-compartment open mammillary model (using the Akaike criterion) with elimination from the central compartment (table III). For the control group, the mean (SEM) values of the distribution and elimination half-lives of propofol were found to be 3.1 (2.03), 43.5 (9.1) and 520 (96) min. There was no statistically significant difference between the two groups for the mean values of the first, second or third phase half-lives. The mean (SEM) central compartment volumes in the control and fentanyl groups were 23.7 (6.6) and 22.8 (5.0) litre, respectively. This shows wide interindividual variability. The mean (SEM) volume of distribution at steady state (V^{ss}) in the control and fentanyl groups were 593 (157) and 996 (453) litre. The mean (SEM) total body clearance of propofol in the control group was 1.61 (0.24) litre min^{-1}, which was similar to that in the fentanyl group (1.89 (0.26) litre min^{-1}). The mean whole blood concentration of propofol did not differ between the two groups throughout the sampling period.

DISCUSSION

The aim of our study was to determine the effect of fentanyl on the pharmacokinetics of a single bolus of propofol in a group of female patients. A significantly greater incidence of apnoea occurred in those who were pretreated with fentanyl. Cockshott and co-workers suggested in 1987 [2] that this effect may be related also to the greater blood concentrations of propofol in this group. Using a similar dosing regimen, in our study we failed to show any difference in the mean blood concentrations of propofol or of the pharmacokinetic variables between the two groups throughout the sampling period. As some calculations in the earlier study were based on four patients, this difference may be explained in part by the larger number studied in our groups introducing a greater variability.

The study by Prys-Roberts [1] used the Cremophor formulation of propofol and also a larger dose of fentanyl (5 μg kg^{-1}). The effects described may have been caused by the formulation of propofol, or the effect of fentanyl may be dose related. The higher incidence of apnoea in the fentanyl group may be a result of the combined apnoeic effect of fentanyl and propofol. In addition, fentanyl may contribute directly to the level of hypnosis which may result in a smaller dose of propofol being required to achieve a given depth of anaesthesia [4, 5]. In our study, both groups received the same dose of propofol.

Gepts and co-workers have shown previously [6] that when propofol was infused at 6 mg kg^{-1} h^{-1} during a computer-assisted infusion of alfentanil (target concentration 300 ng ml^{-1}), the pharmacokinetic profile of propofol did not change. However, propofol induced greater plasma concentrations of alfentanil. It is possible that, instead of fentanyl interfering with the pharmacokinetic profile of propofol, propofol may affect the plasma fentanyl concentrations. Schuttler and colleagues [7] measured etomidate concentrations following administration of etomidate as a bolus dose during steady state (6 ng ml^{-1}) plasma concentrations of fentanyl or enflurane anaesthesia. Much greater plasma concentrations of etomidate were measured over a period of 4 h and the clearance and volume of distribution were reduced by a factor of 2–3 in the fentanyl group. The authors speculated that the reduction in the apparent volume of distribution of etomidate may be a result of displacement of etomidate from tissue binding sites by fentanyl and the reduction in etomidate clearance may be caused by a decrease in liver blood flow and a reduction in its metabolism by either competitive metabolism or inhibition of metabolism. The fentanyl group in their study, however, did not receive the bolus dose of etomidate until 100 min after the start of the fentanyl infusion. These findings have not been confirmed by others. The secondary peaks in blood concentration of propofol at awakening have been described previously [2, 8]. Similar increases in drug concentrations at awakening have been described also for other lipophilic drugs such as fentanyl and thiopentone [9, 10].

Recovery from anaesthesia in our study (median 6 min) was similar in both groups, as were the blood concentrations of propofol at the time of awakening (0.75 μg ml^{-1}). These were similar to the findings of Cockshott and colleagues [2] in those receiving halothane anaesthesia. However, the recovery time for the fentanyl group was shorter, reflecting the slower clearance of halothane. Pretreatment with fentanyl in our study did not appear to influence recovery. It is likely that recovery from anaesthesia in our patients was dependent on the elimination of halothane rather than of propofol.

The systemic clearance of propofol during halothane anaesthesia (1.6 litre min^{-1}) was large and similar to that described by others [2, 8, 11]. In contrast to the findings of Cockshott and colleagues [2] pretreatment with fentanyl did not alter significantly the systemic clearance of propofol or its initial volume of distribution (V_1). The mean values for the $AUC_{0-\infty}$ and AUC_{0-1320} were similar in both groups and to that found by previous studies during halothane anaesthesia, although Cockshott and colleagues showed an increase in $AUC_{0-\infty}$ in their fentanyl group. The variation of some of the pharmacokinetic data was wide, and this may reflect the poor model identification resulting from the secondary peaks seen at awakening. Comparison of the present study with previous studies shows similar values for the γ- and β-phase half-times but $T_{\frac{1}{2}}^{\gamma}$ was greater compared with other studies [2, 8]. The accuracy of $T_{\frac{1}{2}}^{\gamma}$ in these studies must be limited by the sampling period, which was less than twice the terminal elimination half-life. Similar and longer $T_{\frac{1}{2}}^{\gamma}$ of 502 and 674 min have been described by others when sampling was continued for 12 h and 24 h, respectively [11, 12]. The mean initial volume of distribution in both groups (23 litre) was similar to that demonstrated previously [2, 8, 11]. Pretreatment with fentanyl might have been expected to affect the initial disposition of propofol, but our study did not support this fact.

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SPINAL ANAESTHESIA IN DAY-CARE SURGERY WITH A 26-GAUGE NEEDLE

H. QUAYNOR, M. CORBEY AND P. BERG

SUMMARY

We studied 106 day-care surgical patients (52 male) aged 18–70 yr (mean 49.6 yr) who received spinal anaesthesia with a 26-gauge spinal needle. The incidence of headache, back pain and patient acceptability were investigated after operation using a questionnaire. The incidence of postspinal headache was 7.5%, and 11.3% of patients developed back pain. One patient remained in hospital because of hypotension and dizziness. There were no major complications and patient acceptability was almost 100%. We conclude that spinal anaesthesia for day-care surgery is easy to perform and cost effective.

KEY WORDS

Anaesthetic techniques: spinal. Complications: backache, headache. Surgery: day-care.

In our institution nearly 40% of all surgical treatment is performed on a day-care basis. The majority of day-care operations are performed under general anaesthesia, but with the availability of fine gauge needles there is an increasing interest in the use of spinal anaesthesia.

The aim of this study was to investigate the incidence of headache, back pain and patient acceptability in day-care surgical patients following spinal anaesthesia with a 26-gauge needle.

PATIENTS AND METHODS

We studied 106 patients undergoing day-care surgery on the lower half of the body. After the procedure and possible complications had been explained, all patients agreed to receive spinal anaesthesia. One patient failed to return the questionnaire. Four patients were excluded from the study after anaesthesia had been performed by an anaesthetist other than the authors.

TABLE I. *The questionnaire*

1. Did you have backache prior to this present operation?
2. Did you experience backache after the operation?
3. If "yes", was it on the day of operation, 1st day, or 2nd day after the operation?
4. Was the anaesthetic procedure uncomfortable?
5. Was it distressing to be awake during the operation?
6. Did you develop a headache after the operation?
7. If "yes", was the headache on the day of operation, 1, 2 or 3 days after the operation?
8. How many days did your headache last?
9. Did the headache improve with bedrest?
10. Did you take any analgesics? Which? Dosage?
11. Did the treatment help?
12. Would you care to have the same anaesthetic next time?

Patients were premedicated with midazolam 0.07 mg kg^{-1} i.m. and they received Ringer's acetate solution 500–1000 ml before induction of anaesthesia.

Spinal anaesthesia was administered with the patient in the lateral position via the L2–3 or L3–4 interspace after infiltration with local anaesthesia. A 26-gauge spinal needle (Quincke point, Spinocan, Braun, o.d. 0.45 mm) was used without an introducer. Depending on the assumed duration of surgery, hyperbaric lignocaine 75–100 mg, hyperbaric or plain bupivacaine 15–20 mg was injected via the spinal needle.

The ECG was monitored continuously and arterial pressure was measured automatically (Siemans Siracus) throughout surgery. Following surgery, the patients were allowed out of bed as soon as the spinal block had regressed. All patients had a light meal before leaving hospital. Each patient received a questionnaire (table I), and was asked to return it 1 week after operation. On the first day after operation, patients were interviewed by telephone by one of the authors.

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TABLE II. *Spinal anaesthesia in day-care surgery with 26-gauge (Spinocan) needle. Distribution of patients according to age and sex*

	Age (yr)					
	18–25	26–35	36–45	46–65	>65	Total
Male	1	10	14	22	5	52
Female	2	3	15	25	9	54

TABLE III. *Operations performed during the study*

Herniotomy (unilateral)	25
Herniotomy (bilateral)	1
Varicose leg veins (unilateral)	28
Varicose leg veins (bilateral)	8
Hallux valgus osteotomy (unilat.)	27
Hallux valgus osteotomy (bilat.)	12
Spermatocele	2
Orchidopexy	1
Clavus pedis	1
Knee bursa removal	1
Total	106

TABLE IV. *Occurrence of backache with age distribution (overall 11.3%). Numbers in parentheses show number of patients who had backache before lumbar puncture*

	Age (yr)					
	18–25	26–35	36–45	46–65	>65	Total
Male	0	1	3	0	0	4
Female	1	0 (1)	3 (7)	3 (4)	1 (1)	8 (13)

TABLE V. *Occurrence of postspinal headache with age distribution (overall 7.5%). Duration of headache was 1–3 days, treatment with analgesic tablets and bed rest. No patient required blood patch*

	Age (yr)					
	18–25	26–35	36–45	46–65	>65	Total
Male	0	0	1	1	2	4
Female	1	1	0	2	0	4

TABLE VI. *Time of onset and duration of postspinal headache (number of patients)*

	Time of onset		
		After operation	
Duration of headache (days)	Day of operation	Day 1	Day 2
1	—	1	1
2	2	—	—
3	—	2	2

RESULTS

There were 106 patients (52 males). There was a 99% return rate of questionnaires. The majority of patients were in the age groups 36–45 and 46–65 yr (72%) (table II); the type of operations performed is presented in table III.

Twelve patients (11.3%) developed back pain after operation. Of 13 patients with a previous history of backache, eight developed back pain lasting up to 2 days after operation (table IV).

One hundred and four patients (98%) did not find the procedure uncomfortable. One hundred and three (97%) did not find it distressing to be awake during the operation. Some patients developed amnesia after midazolam and remarked that they were "asleep" during the operation.

Eight patients (7.5%) (four men) developed headache, all of which fulfilled the criteria for postspinal headache (table V). One patient had received multiple attempts at three interspaces. The duration of headache was from 1 to 3 days. There was no correlation between the time of onset and duration of postspinal headache (table VI). Headache was relieved by simple analgesics and bed rest in seven patients, and in one patient by bed rest alone. No patient required readmission to hospital or any further therapy.

Five headaches were classified as non-spinal. Three occurred in the time immediately after operation, before the patients were mobilized; two disappeared by the day after operation. Two others developed headache on the day after operation, unaffected by changes in posture.

The distribution of headache did not correlate with the type of anaesthetic used: four patients (two men) developed headache following hyperbaric bupivacaine and the same number following hyperbaric lignocaine.

One hundred and three patients (97%) stated that they would have the same anaesthetic again. Three patients would not like to have the same anaesthesia again; two of these had developed postspinal headache. Only one patient in the study was admitted to hospital, because of hypotension and dizziness. She did not develop headache and was discharged the following day.

None of the patients developed any serious complications and many remarked spontaneously that they were satisfied with the anaesthetic procedure.

DISCUSSION

The incidence of postspinal headache ranges from 3.5% to 45% with 25- and 26-gauge spinal needles, and rates as low as 0.4% have been reported [1, 2]. With 26-gauge "Green pointed" needles, Moore [3] did not find any postspinal headache in 218 patients. It is difficult to explain this large variation in incidence, but several factors such as size of needle, in addition to age and sex of patients, may be significant. With the availability of small calibre needles of 25, 26, 27 and 29 gauges the incidence of headache has been reduced considerably [1, 4]. Rasmussen and colleagues [5] found a greater incidence of postspinal headache in young patients (20–40 yr) when comparing 20- with 25-gauge needles. In a prospective study of young day-care patients, Flaatten and Raeder [6] found an incidence of 37.2% postspinal headache with 25-gauge needles. The incidence of postspinal headache with 26-gauge needles in day-care patients is not known. Burke [7] reported 1.3% headache in 1063 women following laparoscopy under spinal anaesthesia with 26-gauge needles. Day-care patients comprised 23% of this number, but the incidence of headache in this sub-group was not reported.

In our study, headache was defined as postspinal if it was postural, became worse on sitting or standing, and was relieved by lying flat. We found an incidence of 7.5% with 26-gauge needles.

One female, whose headache was included because it fulfilled the diagnostic criteria, admitted that it resembled her usual recurrent headaches. The occurrence of headache did not show any relationship with age or sex, or with the type of spinal anaesthetic used. However, the number of patients studied was small.

The use of an introducer is associated with the risk of accidental dural puncture [8]. However, currently available 26-gauge needles are stiff enough to be used without an introducer.

The same technique was used by all three authors to insert the spinal needle such that the bevel was parallel to the longitudinal fibres of the dura. It has been suggested that this may reduce the incidence of postspinal headache [3, 4, 9].

Bed rest for periods of up to 24 h following spinal anaesthesia is practised commonly, in the belief that this may prevent the occurrence of postspinal headache. Carbaat and van Crevel [10] found in a controlled study that lying in bed for 24 h did not prevent postspinal headache. In a similar study, Cook, Davies and Beavis [11] reported a postspinal headache frequency of 11.6% following a period of only 4 h recumbency after operation, which was not significantly different from that after 24 h recumbency.

Although our study did not examine the effects of bed rest, the low incidence of postspinal headache and the absence of serious symptoms confirm the acceptability of early mobilization after spinal anaesthesia.

The incidence of back pain after spinal anaesthesia is reported to vary between 2% and 26%. Sarma reported an incidence of backache of 9.3% following extradural anaesthesia [12] and Dahl and colleagues [13], using a 20-gauge spinal needle as introducer for a 29-gauge needle, noted a frequency of 26%. Flaatten and Raedar [6] reported a 54.9% incidence of back pain after surgery. Sixty-seven percent of the patients who experienced back pain in this study had a previous history of backache before the operation, which would seem to be a predisposing factor. We used infiltration with local anaesthesia before performing spinal anaesthesia and this may explain our lower incidence of 11.3%.

In establishing a day-care surgical facility, one should consider cost:benefit ratio. In our department, spinal anaesthesia costs 110 Nkr. less than extradural and about 160 Nkr. less than general anaesthesia with short-acting agents.

We conclude that spinal anaesthesia with a 26-gauge needle, is a rapid and reliable technique for day-care surgery with a low incidence of non-serious postspinal headache.

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A COMPUTER DESIGNED GRAPH FOR ADMINISTRATION OF ATRACURIUM BY I.V. INFUSION

D. S. SIMPSON AND A. J. SOUTER

SUMMARY

A bi-exponential mathematical computer model was used to develop a guidance graph for atracurium infusions. The model permitted variation in infusion rates, in pharmacokinetic parameters and in "effect" thresholds. Systematic experiments revealed a relationship between the rate of recovery from a fixed bolus loading dose and the most appropriate initial infusion rate. This relationship was expressed as a guidance graph or "ready reckoner". The quality of guidance was assessed in 50 anaesthetics, given consecutively. In 39 patients optimal myoneural block for surgery was maintained for the duration of the infusion without adjustments or supplementary bolus doses. The mean operating time was 92 min and the mean duration of infusion was 59 min.

KEY WORDS

Neuromuscular relaxants: atracurium infusion. Pharmacokinetics: computer prediction, models.

Atracurium administration by infusion is suitable for long surgical procedures [1–3]. An infusion technique may provide a more controllable effect in which a constant block can be maintained and less agent is used [2]. However, individual infusion requirements may vary and empirical adjustment of the infusion rate to maintain optimal block may be difficult. Haraldsted and colleagues found that about five adjustments in the first 1 h were required for an atracurium infusion sequence [4]. The washin kinetic profile of the drug [5] suggests that 1 h may be required for each upward adjustment, if cumulation is to be avoided. Feedback loop-control systems, in which the level of block can be used to alter the infusion rate, have been proposed [6,7]. These are not yet commercially available, and may be too complex for routine anaesthesia. Harrison [8] measured the duration to recovery of two consecutive test doses of vecuronium and by applying these to formulae, could predict the most suitable infusion rate.

We have developed a system to predict the required rate of atracurium infusion. The system is based on a graph, a form of "ready reckoner" which was developed on a bi-exponential pharmacokinetic model of the drug. The graph relates the time to measured recovery from a single loading bolus of the drug, to the appropriate infusion rate for that patient's kinetic profile and threshold. The administration system is simple and relies only on routine equipment. The purpose of this study was to assess the quality of prediction provided by the graph.

METHODS

Development of the graph

A universal pharmacokinetic computer model was used (see Appendix). This uses a continuously looping mathematical algorithm to translate a given set of pharmacokinetic parameters into an interactive blood concentration curve. The user can impose his own choice of bolus doses and infusion rates and adjust these as the graphically displayed concentration curve unfolds. Therapeutic thresholds may also be displayed. Doses, effect threshold concentrations and the parameters themselves may be altered and overlays may be produced for comparison The model therefore permits many different drug sequences to be given to the same computer patient. By altering the pharmacokinetic parameters and effect threshold concentrations, it also permits different patients to be created, who may then be given the same sequence, for comparison.

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The baseline parameters chosen for this exercise are shown in table I with a threshold concentration derived from work by the same author [9]; figure 1 shows the model's graphic expression of decay of a 35-mg bolus dose, when the shape of decay is determined by these parameters. It can be seen that recovery to a concentration that equates with 90 % single twitch suppression occurred in approximately 26 min. A series of experimental overlays on the model permitted us to determine that an infusion rate of 21 mg h^{-1} would suit the threshold selected. A small, 2-mg supplementary bolus dose is shown, preceding the infusion plateau. This was included to simulate an essential and practical aspect of infusion management. Too rapid a transfer from bolus decay to infusion maintenance would cause a decrease to less than the intended threshold concentration, which might be clinically unacceptable. The inclusion of this dose would not affect the final concentration at equilibrium and, being small, would affect only marginally the time taken to reach that equilibrium.

The parameters and concentration thresholds used in figure 1 are averages. To represent different patients, varying from the average, each figure was altered systematically over a range from approximately 40% less than to 40 % greater than the baseline values (table I). The figure for initial volume of distribution was varied by 80 % to reflect additional differences in patient weight. For each alteration of each element, a 35-mg bolus dose was given to the model, and on recovery to the threshold, wherever it lay, a series of overlays was made, to determine the most suitable infusion rate. Three overlays only are demonstrated for initial volume of distribution in figure 2 and for effect threshold in figure 3. It was clear that giving a fixed bolus to a varying determinant generated a range of different times to recovery and a range of appropriate infusion rates. For each parameter and threshold, a curve could be drawn relating rate of recovery to infusion requirement. This family of curves is shown in figure 4. A crude composite curve (fig. 5) could be drawn, so that for a given return to effect threshold, the rate reading would not be more than a few mg per hour in error, whatever the cause of the variation in shape of decay.

TABLE I. *Atracurium. Two-compartment pharmacokinetic parameters and thresholds. Microconstants derived from slope determinants*

	Weatherley, Williams and Neill [9]	Range of distortion applied to the model
V_1	2.94 litre (70K)	0.6–5.3 litre
k_{10}	7.14 h^{-1}	4.5–10.0 h^{-1}
k_{12}	8.51 h^{-1}	5.0–15.0 h^{-1}
k_{21}	5.65 h^{-1}	3.5–9.0 h^{-1}
90 % single twitch depression threshold		
	1.09 mg $litre^{-1}$	0.65–1.5 mg $litre^{-1}$

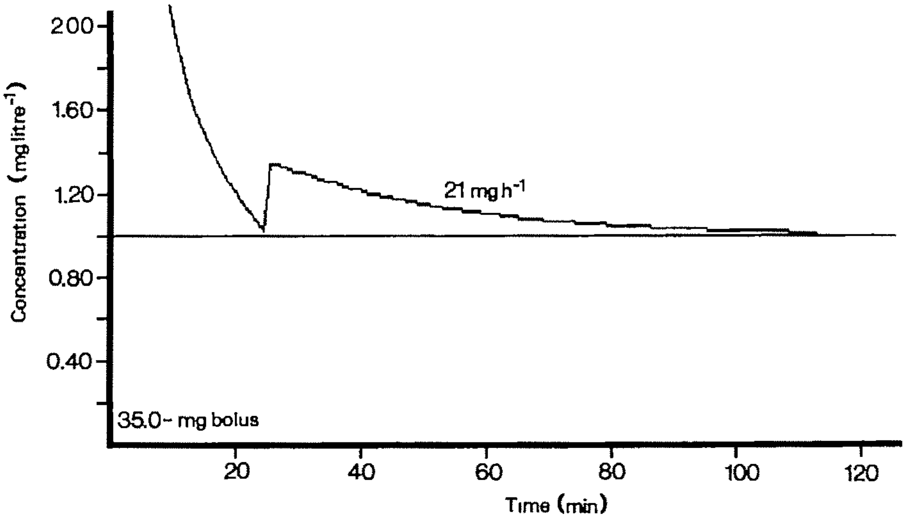

FIG. 1. Print-out from the model of the later part of the decay curve from a 35-mg bolus dose of atracurium with mid-range parameters and thresholds from table I. Experiment showed a 21-mg kg^{-1} infusion rate to be appropriate.

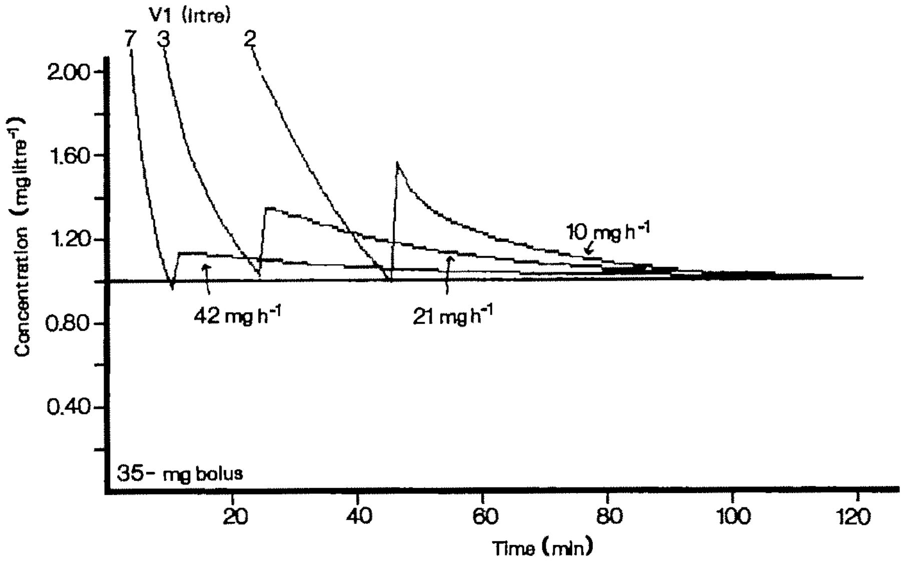

FIG. 2. From left to right superimposed abnormally high (7 litre), normal (3 litre) and low (2 litre) initial volumes of distribution (*V*1), each with 35-mg bolus decay. Infusion rate varied to keep plateaux at threshold value. Reveals different times to recovery and different follow-on infusion rates.

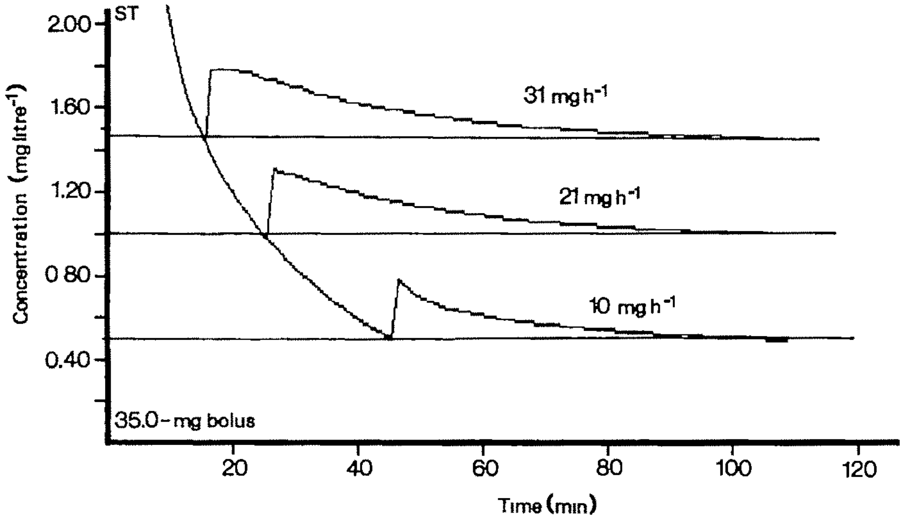

FIG. 3. Three different thresholds of approximately 90 % single-twitch (ST) depression, with the curves for decay of a 35-mg bolus. Different recovery times and different infusion rates to maintain each plateau at threshold.

So far, the graph had been established by varying one determinant at a time and holding all the others steady. One would expect actual patients to have unique sets of parameters and thresholds in which all the elements varied more or less from average values. To reproduce this scatter in a computer test of the curve we generated, in a separate program, 50 sets of randomly abnormal parameters and thresholds in which a distortion of up to 30 % from average was permitted for each value. We thereby had constructed 50 individual theoretical patients, albeit with a flat rather than a "normal" distribution of pharmacokinetic characteristics. Each of these was "given" a 35-mg bolus dose of the drug. When return to the 90 % threshold occurred, the

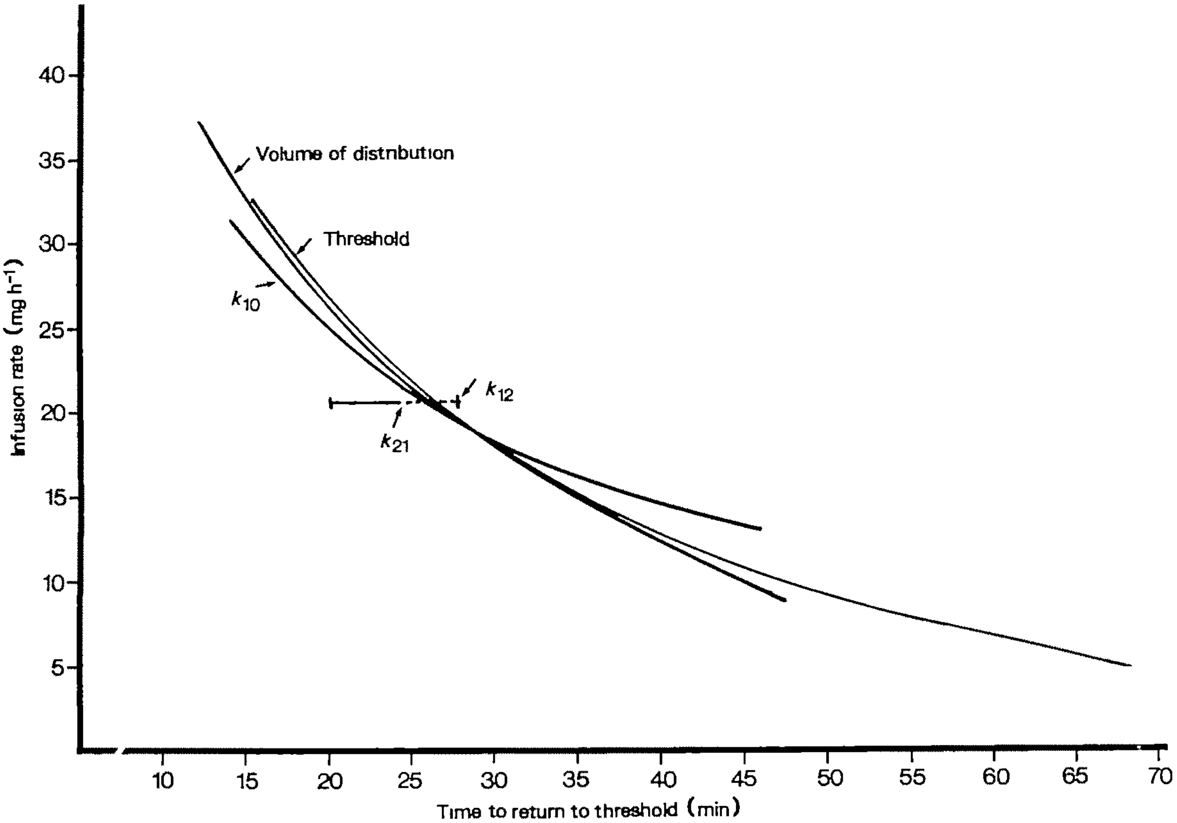

FIG. 4. Family of recovery time–infusion rate curves. Each curve reflects a wide variation in the value of that parameter and relates, across the range, the time to spontaneous recovery to threshold of a 35-mg bolus, with the appropriate infusion rate to maintain concentration at that threshold.

composite curve was consulted to determine the infusion rate. The ensuing concentration plateau at equilibrium was found to approximate to the new threshold without exception.

Finally, the composite curve (fig. 5) was expressed in the form of two different guidance graphs. In one, the loading bolus, as above, was set to 35 mg. In the other the loading dose was set to 0.5 mg kg^{-1}. By removing the effect of weight variation on volume of distribution we could offer an improved choice of loading dose, for unusually large or small patients. This graph proved to be of identical shape but required different labelling. Infusion rates were presented in mg kg^{-1} h^{-1} rather than mg h^{-1}.

Application to patients

Fifty-six anaesthetics given consecutively were allocated in series to two groups of patients according to which expression of the guidance graph would be used. All patients were older than 18 yr and requiring anaesthesia with controlled ventilation for more than 1 h. There was no restriction on ASA category. A requirement for intubation with suxamethonium precluded entry to the study, as did contraindications to atracurium, or to any component of the selected background anaesthetic sequence. The study was approved by the local Ethics Committee.

Each patient received an opioid premedication and routine induction of anaesthesia with thiopentone. For maintenance, nitrous oxide and 1% enflurane in oxygen were administered for the first 10 min, after which the enflurane was reduced to 0.4%. Supplements of opioids and droperidol were given where indicated. Ventilation was adjusted to produce normocapnia, and all i.v. fluids were warmed.

Twenty-seven patients were given atracurium 0.5 mg kg^{-1} as a bolus dose at induction, and 29 were given a fixed dose of 35 mg, irrespective of weight. A stopwatch was started. A nerve stimu-

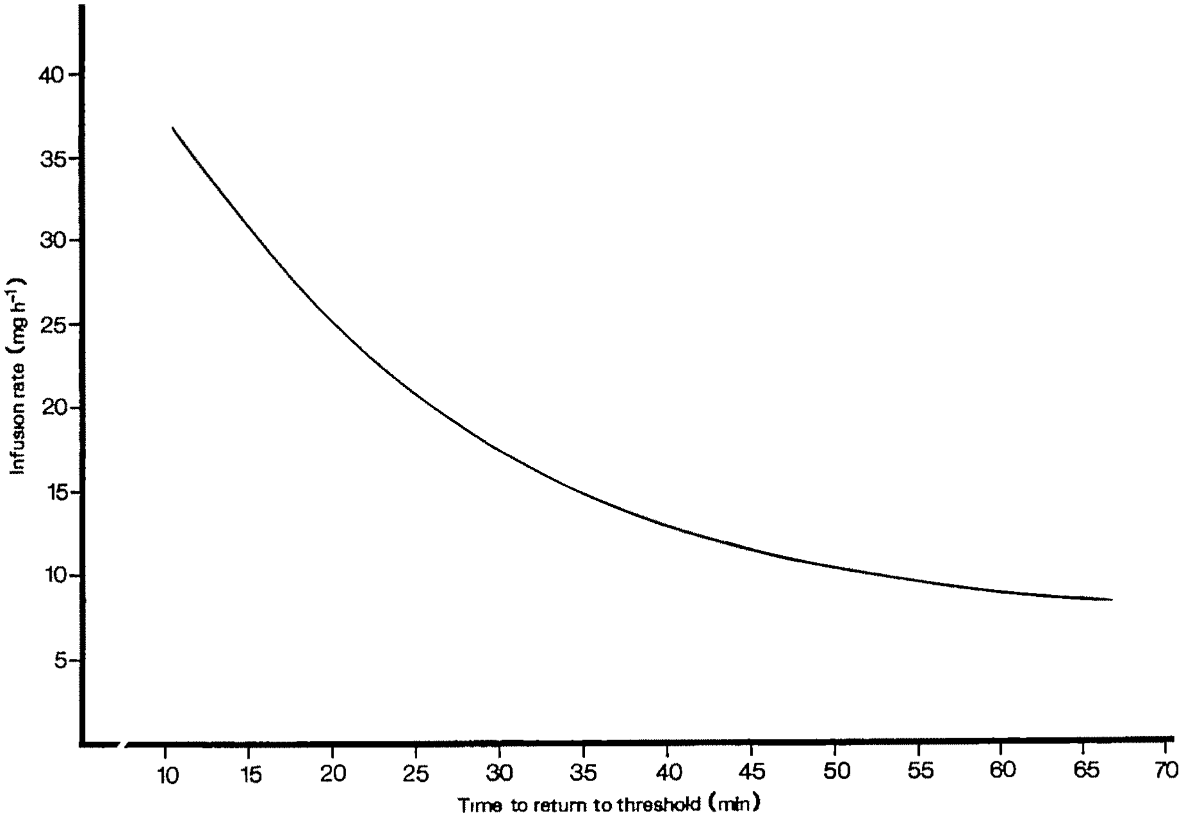

FIG. 5. Composite curve of figure 4: 35-mg bolus dose "guidance graph".

lator was attached to the ulnar aspect of the wrist. Intermittent trains of four supramaximal stimuli (0.2 ms and 2 Hz) were applied and tactile assessment made of the train-of-four (TOF) responses of the adductor pollicis. The times to return of T1 and T2 were recorded. On the return of the second response a small "holding" bolus of 2 mg was given while the appropriate guidance graph was consulted and the infusion prepared and started. A 4-mg bolus was given if the recovery occurred earlier than 30 min.

Thereafter, and for the duration of the operation, myoneural assessment was made at 5-min intervals. A period of 100% depression was expected for the first 15 min following the supplementary bolus, but thereafter the presence of one or two TOF responses, only, was deemed acceptable. If the responses disappeared, or if more than two returned, intervention was indicated; the infusion was stopped or a further bolus given. In such cases, the guidance provided by the graph was considered to be a failure. When it was judged that the operation was within 10 min of completion, the infusion was stopped, as was the administration of enflurane. The time and the TOF response were noted at the end of surgery.

RESULTS

In six patients no infusion was given. Two failed to become blocked adequately from the loading dose and in four more the operation was finishing before the infusion was started. In two of the four this was because the operation was of a shorter duration than expected, and in the other two it was because of an unusually long recovery time.

The remaining 50 patients were allocated equally between the two studies, providing 25 "guided" infusions for each type of graph. Both studies are included in the results, together with the totals, so expressing the independence of each type of graph and an overall measure of the technique as a whole. Table II shows the average duration of operation, the average duration of the

TABLE II. *Duration of operations and infusions (mean (range)). Mean weights and ages of patients*

	0.5-mg kg^{-1} bolus	35-mg bolus	
	25 patients	25 patients	50 patients
Duration of operation (min)	92.6 (54–166)	91.8 (52–250)	92.2
Duration of infusion (min)	56.4 (21–133)	62.0 (19–232)	59.2
Weight (kg)	66.6	73.3	69.9
Age (yr)	51.6	57.2	54.4

TABLE IV. *Mean* (SD) *times to recover to a TOF count of 2 and infusion rates prescribed*

	0.5-mg kg^{-1} group	35-mg group	Total
Time to return to TOF 2 (min)	36.0 (9.0)	29.3 (7.3)	32.6 (8.9)
Infusion rate (mg h^{-1})	18.2 (4.2)	21.4 (6.0)	19.8 (5.5)
Infusion rate (mg kg^{-1} h^{-1})	0.28 (0.07)	0.29 (0.09)	0.29 (0.08)

infusions, and the weights and ages of the patients.

Table III presents the outcome. In the 0.5-mg kg^{-1} bolus group there were 10 patients in whom, following the setting of the infusion, only a single TOF response was palpable for the duration of the operation. In a further nine patients a second response became palpable at some stage. There were five patients in whom a third response became evident at some time, but in two this occurred so near the end of the procedure that no intervention was indicated. Three of 25 patients required intervention with an additional bolus, because of the recovery of a third response. The infusion had to be stopped, temporarily, in only one patient, because all responses disappeared. Results were similar for the 35-mg bolus group. In total, 42 of 50 patients required no adjustment of the infusion throughout the duration of the operation.

The mean duration of infusion for each category is also included in table III. Thirty-nine patients showed an acceptable level of block for the duration of the operation and the mean duration of infusion in this group was 54 min. This compared with a mean duration of infusion of 71 min for those 11 patients whose block eventually became less than optimal. This difference between the two groups was not significant ($P > 0.05$).

Table IV records the average time to recovery from the loading bolus, with the infusion rate (mg kg^{-1} h^{-1}). This last value was computed retrospectively in the 35-mg bolus group.

As time progressed there was a decline in the number of operations still running, which is represented in figure 6. At each stage, the shaded area shows the proportion of those in which an acceptable level of block was maintained without any intervention.

DISCUSSION

The use of two-compartment open model parameters is controversial. Atracurium, in particular, is not eliminated exclusively from the central compartment [10], and all neuromuscular blocking drugs may be represented better with an additional effector compartment [11]. However, open model parameters are derived from the mathematical determinants of a blood concentration curve. As such, they may be viewed as simple determinants of the size and the shape of that curve. If they are varied, the shape of the curve is varied.

Our approach to pharmacodynamics may have

TABLE III. *Train-of-four profiles throughout operations. Last two columns display number of patients for whom adjustment of infusion was required*

	T1 only	T1 and T2 only	T3	T3 intervention	T0 intervention
0.5 mg kg^{-1}	10	9	2	3	1
35-mg bolus group	13	7	1	3	1
Totals	23	16	3	6	2
Duration of infusion (SD) (min)	40.3 (20)	74.7 (24)	61.0 (38)	66.8 (14)	127.0 (105)

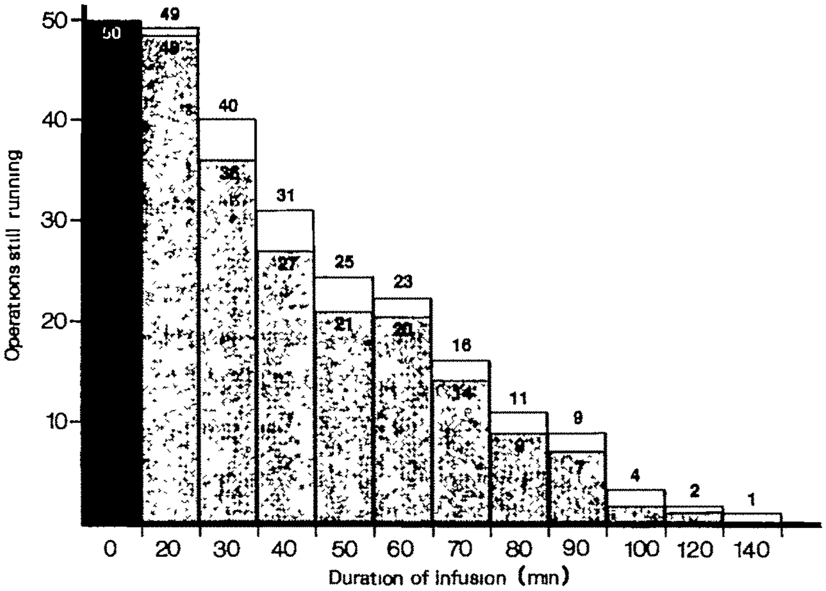

FIG. 6. Decrease in number of infusions still running as time passed, and the operations ended. Stippled area shows proportion remaining optimally blocked without adjustment to the infusion.

been excessively simple. We addressed, on the model, only a variable blood concentration threshold, albeit over a rather wide range. In principle, the concentration which pertained at the myoneurally measured point in the initial decay is unknown, but presumed to be between 0.3 mg litre^{-1} and 1.5 mg litre^{-1}. Whatever it is, our system is computed to preserve it, by means of the guided infusion. The system is, then, essentially independent of the type of myoneural monitoring or its response value, provided an approximate "surgically optimal" myoneural response is selected. A multiple post-tetanic count [12] or a TOF count of 1, might serve as well. Our choice of the second, rather than the first, TOF response as our benchmark of loading dose recovery and maintenance was important. Some patients do not lose T1 when given atracurium 35 mg.

Significant hysteresis characterizes the relationship between blood concentration and effect [9, 11]. For atracurium this is particularly so immediately after a bolus dose (effect less than expected) and in the early to mid part of decay (effect more than expected). We tried to restrict our measures and manipulations on the model to the later parts of the decay curve and the steady state, where there is good correlation between blood concentration and effect [9].

The graph we produced related the time to recovery of a single bolus dose of the drug to the approximate infusion rate required to maintain optimal block. The relationship was crude, and there was little place for precision in the clinical assessment of its accuracy. We chose a practical framework for the study. It was felt that the system would either work, in practice, with a simple peripheral nerve stimulator or it would have little to contribute to routine anaesthesia. However, a considerable measure of good guidance was evident. In 42 of 50 operations, lasting an average 92 min, the initial infusion setting required no adjustment.

It is clear that during longer operations it was less likely that optimal block would be maintained throughout (table III). More time is available for inaccuracy to become evident, and for the infusion plateau to slip out of the therapeutic window. In addition, longer operations imply more intraoperative physiological change, caused by blood loss, hypothermia or acidosis. In general, we were surprised that an infusion prediction made early in the procedure should hold good, for so long, in most of the patients studied.

Our infusion rates, when related retrospectively to weight, proved to be less than those of other workers. Eager, Flynn and Hughes [2] revealed a range of 0.29–0.49 mg kg^{-1} h^{-1}; Hutton's figures

[6] were 0.29–1.01 mg kg^{-1} h^{-1} and Webster and Cohen [7] found a rate of 0.48 mg kg^{-1} h^{-1} for precise control at T1 level. Our findings of 0.29 mg kg^{-1} h^{-1} may be explained by the enhancing effect of enflurane on neuromuscular block [13]. The scatter of infusion rate requirements in each study confirms the work of others and justifies the development of a prediction formula.

The sequence, in which a fixed 35-mg loading bolus was used to "prime" the graph, was successful. In our view, this provides the basis of an extremely simple and practical prescription. Calculations of milligrams per kilogram are not required, nor are unusual dilutions or doses. The patient's weight need not be known. The guidance for infusion rate is provided simply in terms of milligrams per hour, and appears to account for individual patient requirements.

APPENDIX

UNIVERSAL PHARMACOKINETIC MODEL—DESCRIPTION

The program is written in BBC Basic occupying about 30 k. It is an educational tool, which permits a user to construct, for any drug, a blood concentration–time decay curve, which is displayed on the screen. The passage of time is accelerated approximately 60-fold on the model, and can be temporarily "frozen" at any point, as the curve unfolds, to permit interaction by the prescription of i.v. boluses or infusion adjustments, or both.

Initially, the user is required to select a two-compartment or a three-compartment model, and then to provide a set of pharmacokinetic parameters which he will have acquired, usually, from the medical literature. *V*1, the central compartment volume is required, and k_{10}, the central elimination microconstant, and either two or four peripheral compartment time microconstants, according to which type of model has been selected. Mathematically, peripheral compartment volumes are not required. The time range over which the curve will run can be selected, and the theoretical patient weight is required. The units required for the concentration display must be selected, and a threshold concentration or therapeutic window can be chosen, and displayed, which offers a target or reference for a developing concentration curve.

The user is then invited to "inject" a bolus or start an infusion, or both. The program calculates the most appropriate concentration range to display and offers this option for confirmation. The decay (or washin) curve then unfolds on the screen, and can be compared with threshold values and adjusted, if required, by adding boluses or adjusting the infusion. Concentrations and time passed are displayed digitally and graphically. Also, there is a digital display of the end-point concentration that would be expected at equilibrium and the infusion rate which would be required to achieve threshold concentrations.

At any stage, the experiment can be halted and an overlay curve constructed with a new sequence of therapy. If required, the pharmacokinetic parameters can be altered for each new overlay.

Well derived sets of pharmacokinetic parameters, when obtained in the literature, are precious, and repeatedly feeding them in to the model can be tedious. A complementary, integrated filing program is included therefore, so that sets of microconstants can be saved. These may be loaded directly to the model, at a later date. A housekeeping facility allows the files to be displayed and selected in a menu-driven format In addition, slope and intercept type bi- or tri-exponential determinants can be entered, and the appropriate calculations performed to convert these to microconstants before saving them to the files.

The key element of the two-compartment option is the mathematical algorithm that repeats a calculation of central and peripheral concentrations every 10 model seconds. This requires the solution of two quadratic equations. The central concentration, calculated, is then used to update the curve:

```
 90  DEF PROC 2COMPMATHS
100  rem, R = infusion rate
110  rem, P2 = time passed, P1 = time interval
120  rem, NC1 = central concn at start of interval
130  rem, NC2 = periph concn at start of interval
140  rem, C1 = developed central concn
150  rem, C2 = developed periph concn
160  P2 = P2+P1   rem, updates time progress
170  T = P1/6   rem, time interval of 10 s
180  Z = R/V1* Weight
190  B = K10+K12+K21
200  a = (B+(sqr((B*B)-(4*K21*K10))))/2
210  b = (B-(sqr (B*B)-(4*K21*K10))))/2
230  Y1 = (NC1*K21)+(NC2*K12)+Z
240  Y2 = (NC2*(K12+K10))+(NC1*K21)
250  A = (NC1*a*a)-(Y1*a)+(Z*K21))/(a*(a-b))
260  B = ((NC2*a*a)-(Y1*b)+(Z*K21))/(b*(b-a))
270  L = ((NC2*a*a)-(Y2*a)+(Z*K21))/(a*(a-b))
280  M = ((NC2*b*b)-(Y2*b)+(Z*K21))/(b*(b-a))
290  C1 = (A*EXP(-a*T))+(B1*EXP(-b*T))+(Z/K10)
300  C2 = (L*EXP(-a*T))+(M*EXP(-b*T)+(Z/K10)
310  NC1 = C1: NC2 = C2   rem, new concns now starting
     concns.
320  PROC GRAPH (C1)   rem, sends C1 to the updating display
     procedure
330  ENDPROC
```

The algorithm for the three-compartment option is significantly more complex, but was not used for this study.

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DOSE REQUIREMENTS AND PLASMA CONCENTRATIONS OF PIPECURONIUM DURING BILATERAL RENAL EXCLUSION AND ORTHOTOPIC LIVER TRANSPLANTATION IN PIGS

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SUMMARY

We have studied five pigs undergoing bilateral clamping of the renal pedicles, seven pigs undergoing orthotopic liver transplantation and three control animals without surgery in order to examine the roles of the kidney and liver in the plasma clearance of pipecuronium. An i.v. infusion of pipecuronium was controlled to maintain a constant 90–95% twitch depression throughout the investigation. The right sciatic nerve was stimulated continuously with supramaximal stimuli at 0.1 Hz and the force of the corresponding evoked isometric muscle contraction was recorded continuously. Control pigs needed an infusion rate of pipecuronium 8–10.7 µg kg^{-1} *min*$^{-1}$*. In the renal group, it was necessary to reduce the infusion rate of pipecuronium by about 25% after clamping both renal vascular pedicles (*$P < 0.05$ *compared with controls); in pigs undergoing liver transplantation, it was necessary to reduce the rate by approximately 80% after clamping hepatic vessels (*$P < 0.05$ *compared with controls and from the period after clamping of renal vessels). After hepatic recirculation, the infusion rate of pipecuronium was increased progressively to a rate which corresponded to 50% of baseline values (*$P < 0.05$ *compared with the anhepatic phase and from controls). Plasma concentrations of pipecuronium were comparable in the three animal groups and did not change significantly during the study. These data suggest that the liver plays a more important role than the kidney in the plasma clearance of pipecuronium in pigs.*

KEY WORDS

Neuromuscular relaxants: pipecuronium Pharmacokinetics: pipecuronium, liver transplantation, renal function.

Pipecuronium bromide is a new long acting non-depolarizing steroidal neuromuscular blocking drug, which has pharmacodynamic and pharmacokinetic profiles similar to those of pancuronium, but without cardiovascular side effects [1–3]. In patients without renal function, plasma clearance of pipecuronium remains at 60% of normal values, suggesting that only 40% of an administered dose is dependent on the kidneys for its elimination [4]. There are no data available on the role of the liver, except for one animal study in rats indicating minimal hepatic elimination [5].

To evaluate the roles of the kidney and the liver on the dose requirement of pipecuronium, we have measured the rate of infusion and the corresponding plasma concentration of pipecuronium necessary to maintain a steady state neuromuscular block before and after ligature of the renal vascular pedicles, and with and without the liver during orthotopic liver transplantation in pigs.

METHODS

Fifteen pigs (*Sus scrofa* domesticus) weighing 22–25 kg were included in the study, after approval of the Ethics Committee on animal research of our institution. Animals were allocated to three groups: group A as control group ($n = 3$), group B undergoing ligature of both renal vascular pedicles ($n = 5$), and group C undergoing ortho-

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topic liver transplantation ($n = 7$). Animals from the control group underwent identical monitoring and anaesthesia, but without surgery.

Procedure

Each animal received azaperone 4 mg kg^{-1}, ketamine 7.5 mg kg^{-1} and fentanyl 2 µg kg^{-1} i.m. 30 min before anaesthesia comprising 2–3% isoflurane in oxygen. The trachea was intubated without the use of neuromuscular block and anaesthesia was maintained with 0.5% isoflurane in oxygen and fentanyl 4 µg kg^{-1} h^{-1}. Ventilation was controlled to keep arterial $P\text{CO}_2$ at 5.0–5.5 kPa, and body temperature was maintained at 36.0–37.5 °C with thermoblankets. Normal saline was infused i.v. through a jugular vein at 10 ml kg^{-1} h^{-1}. Mean systemic arterial pressure and central venous pressure were measured using a carotid arterial cannula and a central venous catheter, respectively, and calibrated pressure transducers (1290 A Hewlett–Packard) positioned at the mid-axillary line, and were recorded on a chart recorder (Hewlett–Packard, 78172 A). Arterial pH was maintained at 7.35–7.50 (with sodium bicarbonate, if necessary). The right posterior leg of the pig was immobilized and the sciatic nerve was isolated surgically in the popliteal space. Using a nerve stimulator (Laubscher P1 NS-2B), continuous supramaximal stimulation of 0.2 ms duration at 0.1 Hz frequency was applied directly to the nerve branch supplying the tibialis anterior muscle. The corresponding evoked isometric contraction of the tibialis anterior muscle was recorded continuously by a Grass FT-10 force-displacement transducer on a one-channel recorder (Kipp and Zonen BD 8). After stable anaesthesia had been established for at least 30 min, a single i.v. bolus injection of pipecuronium of 150 µg kg^{-1} was administered, followed 5 min later by an i.v. infusion of pipecuronium delivered by an infusion pump (Vickers Medical, Model SP55) and adjusted continuously to maintain a constant 90–95% twitch depression. The initial bolus dose of pipecuronium ($\text{ED}_{95} = 150 \pm 20$ µg kg^{-1}) was determined by a cumulative dose technique in a preliminary study in five pigs. Blood samples for measurement of pipecuronium concentrations were drawn every 15 min, from 30 min after the beginning of pipecuronium infusion to the end of operation.

In animals undergoing bilateral renal exclusion, both renal vascular pedicles were prepared, and after a 60-min period of stabilization during which neuromuscular function was recorded, the pedicles were ligated and divided. The laparotomy was closed and the animals were studied during the following 120 min. In animals undergoing orthotopic hepatic transplantation with a second donor liver, the surgical procedure consisted of three parts. The first phase corresponded to the preparation of the vessels for insertion of the cavo–porto–jugular bypass and dissection of hepatic ligaments and vessels to allow the hepatectomy. During the anhepatic (second) phase, splanchnic blood was drained into the internal jugular vein using an external active non-occlusive veno–venous bypass (BP 50 Biomedicus, Minnesota, U.S.A.). The bypass had a priming volume of 320 ml, flow rate of 1000 ± 200 ml min^{-1} and ejection pressure of 100–120 mm Hg. The third phase consisted of the period after recirculation of the graft during which end-to-end anastomosis of the hepatic artery and cholecystoduodenostomy were performed.

Measurement of plasma concentrations of pipecuronium

One millilitre of whole blood was collected in a heparinized tube and centrifuged immediately at 5000 *g* for 30 s; 500 µl of plasma was transferred into an Eppendorf tube and frozen quickly to −70 °C in acetone and dry ice. Samples were stored at −70 °C until analysed. Plasma concentrations of pipecuronium were measured by a new technique using iodine-labelled bengal rose [6]. This technique consists of producing a complex between pipecuronium and iodine-labelled bengal rose. By comparison with an appropriate calibration curve, measurement of radioactivity of this complex permits measurement of pipecuronium. The use of ^{125}I-bengal rose with a specific activity of 150 µCi mg^{-1} permitted measurement of pipecuronium to a detection limit of 5 ng ml^{-1}. This assay is linear over the range 5–5000 ng ml^{-1}, with a correlation coefficient of 0.99 in pig plasma. Inter-assay coefficients of correlation (for 10 assays) were 16.1% at 10 ng ml^{-1} and 5.4% at 100 ng ml^{-1} of pipecuronium. Intra-assay coefficients of correlation (for 10 assays) were 10.5% at 10 ng ml^{-1} and 3.2% at 100 ng ml^{-1} of pipecuronium. Metabolites of pipecuronium and other anaesthetic agents do not interfere with measurement of pipecuronium concentrations [7].

Statistical analysis

In each animal group, recorded variables over time were compared by one-way analysis of variance for repeated measurements followed by Bonferroni's multiple comparisons test; comparisons between the three animal groups were made using a one-way analysis of variance followed by a Duncan's multiple comparisons test. For all statistical comparisons, differences were considered significant if $P < 0.05$.

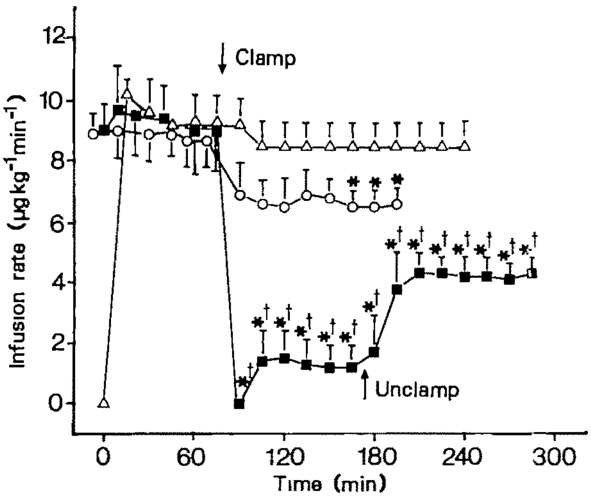

FIG. 1. Mean infusion rate of pipecuronium adjusted to maintain a stable 90–95 % twitch depression in three control pigs (△), in seven pigs undergoing orthotopic liver transplantation (■), and in five pigs undergoing bilateral renal exclusion (○). Data points represent mean (SEM) of values measured every 15 min. Clamp = clamping of renal and hepatic vessels; Unclamp = restoration of hepatic circulation. $P < 0.05$: *compared with control; †compared with pigs with bilateral renal exclusion.

RESULTS

Pipecuronium-induced neuromuscular block was stable at 90–95 % twitch depression in each animal of the three groups during the entire investigation. In control animals, a mean infusion rate of pipecuronium of 8.3 μg kg^{-1} min^{-1} (range 8–10.7 μg kg^{-1} min^{-1}) was necessary to maintain neuromuscular block at 90–95 % twitch depression during the 240-min study period (fig. 1). To maintain a similar neuromuscular block in pigs with bilateral renal exclusion, a mean infusion rate of pipecuronium of 8.9 μg kg^{-1} min^{-1} (range 7–11 μg kg^{-1} min^{-1}) was necessary before clamping both renal pedicles (ns at each time interval compared with control animals). After exclusion of both kidneys, the infusion rate had to be reduced significantly within 15 min to mean 6.9 (SEM 0.8) μg kg^{-1} min^{-1} ($P < 0.05$ compared with the period before clamping of renal vessels), and it remained at this lower rate for the 2 h to the end of the study. To maintain block at 90–95 % twitch depression in pigs undergoing liver transplantation, the mean infusion rate of pipecuronium was 9.3 μg kg^{-1} min^{-1} (range 6–12 μg kg^{-1} min^{-1}) during the period before clamping of hepatic vessels (ns at each interval time compared with control animals). After clamping of liver vessels, we observed a rapid increase in the neuromuscular

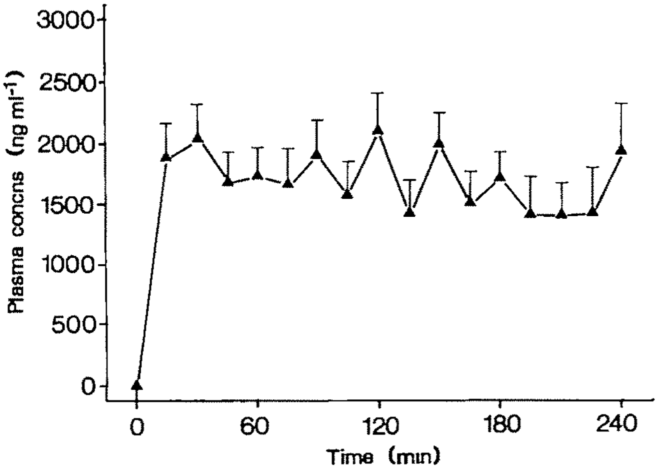

FIG. 2. Plasma concentrations of pipecuronium during a 240-min i.v. infusion of pipecuronium adjusted to maintain a stable 90–95 % twitch depression in control pigs. Data points represent mean (SEM) of three animals measured every 15 min.

block (up to 100%), despite reduction in the infusion rate. In order to restore 90–95% neuromuscular block rapidly, we stopped the infusion for a short time (10–15 min) and subsequently the infusion rate of pipecuronium was maintained at 1.2 (0.5) and 1.5 (0.7) μg kg^{-1} min^{-1} up to recirculation of the liver ($P < 0.05$ for each data point compared with the period before clamping of hepatic vessels, controls and the period after clamping of renal vessels) (fig. 1). To maintain a comparable neuromuscular block after restoration of the circulation to the liver, the mean infusion rate of pipecuronium was increased progressively over 45 min to 4.3 (0.4) μg kg^{-1} min^{-1} and maintained at these values during 60 min up to the end of the study. These infusion rates were significantly ($P < 0.05$) greater than those during the anhepatic phase, but significantly ($P < 0.05$) less than those during the period before exclusion of the liver.

Plasma concentrations of pipecuronium in the control group remained between 1416 (365) ng ml^{-1} (smallest) and 2098 (299) ng ml^{-1} (greatest) with a mean value of 1783 ng ml^{-1} and did not change significantly during the 240-min study period (fig. 2).

Before and after bilateral renal exclusion, plasma concentrations of pipecuronium remained between 1241 (105) ng ml^{-1} (smallest) and 1677 (212) ng ml^{-1} (greatest) with a mean value of 1460 ng ml^{-1} (ns compared with control group) and did not change significantly during the entire investigation, despite a 120-min duration of bilateral renal exclusion (fig. 3).

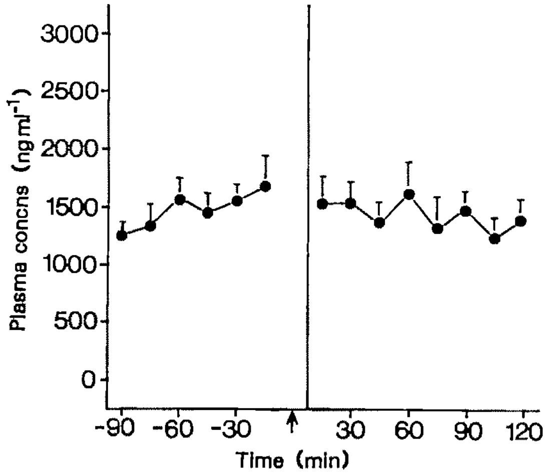

FIG. 3. Plasma concentrations of pipecuronium before and after bilateral renal exclusion (↑) in pigs receiving an i.v. infusion of pipecuronium adjusted to maintain a stable 90–95% twitch depression. Data points represent mean (SEM) of five animals measured every 15 min, and were not statistically different over time (two-way ANOVA).

Plasma concentrations of pipecuronium during the three different phases of liver transplantation remained between 1332 (257) ng ml^{-1} (lowest) and 2513 (620) ng ml^{-1} (greatest) with a mean value of 1988 ng ml^{-1} (as compared with control group) and did not change significantly during the entire investigation, despite a 90-min duration of liver exclusion (fig. 4).

Rectal temperature was maintained in the control group at 38.0 ± 0.1 °C, during the three phases of liver transplantation (before liver ex-

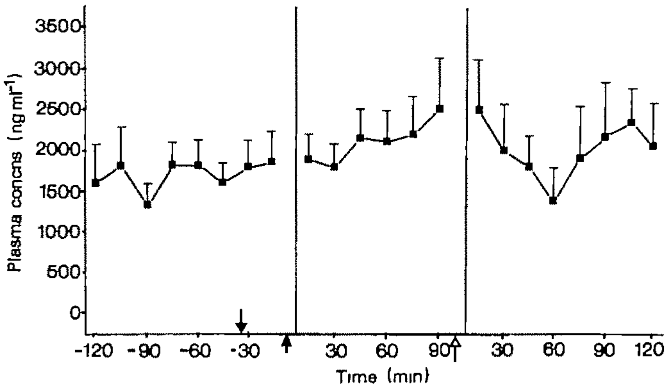

FIG. 4. Plasma concentrations of pipecuronium during the three phases of orthotopic liver transplantation in pigs receiving an i.v. infusion of pipecuronium adjusted to maintain a stable 90–95% twitch depression. ↓ = Crossclamp of hepatic artery; ↑ = crossclamp of portal vein; ⇧ restoration of hepatic circulation. Data points represent mean (SEM) of seven animals measured every 15 min, and were not statistically different over time (two-way ANOVA).

TABLE I. *Time course, haemodynamic variables,* Pa_{CO_2}*, arterial pH, and rectal temperature (mean (SEM)) in the three groups of animals. MAP = Mean arterial pressure; CVP = central venous pressure.* $P < 0.05$: **compared with before crossclamping of liver vessels; †between control group and the period before crossclamping of liver vessels*

		Liver transplantation			Renal exclusion	
	Control	Before clamping liver vessels	Anhepatic phase	After hepatic recirculation	Before clamping renal vessels	After clamping renal vessels
Duration (min)	240	128 (7)	95 (5)	122 (10)	90	120
Heart rate (beat min^{-1})	118 (6)	112 (5)	113 (5)	151 (5)*	115 (6)	113 (7)
MAP (mm Hg)	69 (2)†	92 (3)	78 (3)	88 (3)	74 (6)	72 (5)
CVP (mm Hg)	2 (1)	2 (1)	2 (1)	3 (1)	3 (1)	3 (1)
Pa_{CO_2} (kPa)	4.7 (0.13)	4.5 (0.13)	4.7 (0.13)	4.8 (0.13)	4.8 (0.13)	4.7 (0.13)
Arterial pH	7.41 (0.01)	7.43 (0.01)	7.38 (0.01)*	7.35 (0.01)*	7.43 (0.01)	7.41 (0.01)
Rectal temperature (°C)	38.0 (0.1)	37.8 (0.1)	37.9 (0.1)	37.6 (0.1)	37.9 (0.1)	37.8 (0.1)

clusion: 37.8±0.1 °C; during cross-clamping: 37.9±0.1 °C; after liver recirculation: 37.6 ±0.1 °C) and in animals undergoing bilateral clamping of renal vessels (before kidney exclusion: 37.9±0.1%, after kidney exclusion: 37.8±0.1 °C). Arterial pH remained stable in control animals (7.41±0.01) and in animals with bilateral renal exclusion (before kidney exclusion: 7.43±0.01; after kidney exclusion: 7.41±0.01) during the entire study period. In animals undergoing liver transplantation, arterial pH decreased significantly ($P < 0.05$) during the anhepatic phase compared with the period before clamping of hepatic vessels (7.43±0.01 *vs* 7.38±0.01, respectively) and remained at values less than control after restoration of the hepatic circulation (7.35±0.02).

In the control group and in animals with bilateral renal exclusion, the cardiovascular variables remained within 20% of baseline during the entire investigation (table I). In animals undergoing liver transplantation, mean systemic arterial pressure and central venous pressure did not change significantly during the three phases of liver transplantation. In contrast, these animals developed significant tachycardia after restoration of hepatic circulation (from 112±5 to 151±5 beat min^{-1}) ($P < 0.05$).

DISCUSSION

The results of the present study demonstrate that in pigs, bilateral renal exclusion and absence of the liver produced respectively 25% and 80% decreases in the dose requirement of pipecuronium necessary to maintain constant neuromuscular block without significant change in plasma concentrations of pipecuronium. This indicates that the liver plays a more important role than the kidney in plasma clearance of this agent in pigs.

To determine plasma concentrations of pipecuronium, we used a new method based on the production of a complex between pipecuronium and iodine-labelled bengal rose [6]. This assay is specific for the parent compound and does not measure metabolites of pipecuronium. It has detection limits less than those of the colorimetric assay described earlier [7, 8] and gives results comparable to those of the recently published capillary gas chromatographic assay for quaternary ammonium steroidal neuromuscular blocking agents [9].

In control animals, administration of a 150-μg kg^{-1} bolus and of a 8.3-μg kg^{-1} min^{-1} constant rate i.v. infusion of pipecuronium allowed us to produce and maintain a stable 90–95% twitch depression, which was associated with stable plasma concentrations of pipecuronium during the entire study. Doses of pipecuronium used in this study in pigs were twice the dose necessary in humans [10]. This high requirement for myoneural blockers in pigs has been reported for other drugs, such as atracurium [11], vecuronium and gallamine [12].

To maintain a similar twitch depression in animals undergoing ligature of both renal vascular pedicles, before renal exclusion we needed an infusion rate of pipecuronium comparable to that required in control animals. Plasma concentrations of pipecuronium measured before clamping of renal vessels were also comparable to those determined in the control group. Similarly, infusion rate and plasma concentrations of pipecuronium measured before crossclamping of hepatic vessels were comparable to those measured in control animals. These findings suggest that our control animals may be considered as true controls, although they did not undergo surgery. Isoflurane anaesthesia (1 MAC) alone does not modify hepatic blood flow [13], and isoflurane in a concentration similar to that used in the present study in association with surgical stress (laparotomy) produces only a small decrease in hepatic blood flow [14].

Exclusion of both kidneys produced a 25% reduction in dose requirement of pipecuronium. Despite significant reduction in infusion rate, plasma concentration of pipecuronium remained stable. Our data are comparable to the 34% reduction in plasma clearance of pipecuronium observed in patients undergoing cadaver renal transplantation [4] compared with clearance in patients with normal renal function. In contrast, in dogs studied 1 h after bilateral renal exclusion, an 85% reduction in plasma clearance of pipecuronium was observed in comparison with control animals [15]. These differences probably reflect species variation.

Exclusion of the liver produced an 80% reduction in dose requirements of pipecuronium necessary to maintain similar neuromuscular block as that before clamping of liver vessels without significant changes in plasma concentrations of this agent. Many factors may explain this change. We did not evaluate renal function of our pigs undergoing liver transplantation but urine output was maintained at values greater than 1 ml kg^{-1} h^{-1} during the entire investigation, and we found a maximal decrease in dose requirements of pipecuronium, after bilateral renal exclusion, of only 25%. Therefore, it is unlikely that changes in renal function alone could explain this decrease in dose requirement. Other important factors affecting pharmacodynamics, such as systemic haemodynamics, temperature or blood pH, remained within the physiological range during the period of liver exclusion. Increased receptor sensitivity and a decrease in volume of distribution of pipecuronium induced by exclusion of the liver could also be evoked. However, during the anhepatic phase, we used an external veno-venous bypass to allow drainage of the splanchnic circulation which represents an important part of the total blood volume in pigs, avoiding possible changes in volume of distribution of pipecuronium. In a previous study, we used the same animal model to investigate atracurium, a neuromuscular blocking drug known to be independent of the kidneys and liver for its elimination [11]. We have found that plasma concentrations and infusion rates of atracurium did not change significantly during the anhepatic phase compared with the period before clamping of the hepatic vessels. In contrast, plasma concentrations of its metabolite laudanosine, known to be metabolized in the liver, increased significantly after exclusion of the liver compared with the period before clamping of the hepatic vessels. Therefore, it is unlikely that increased sensitivity of the neuromuscular junction during the anhepatic phase could explain our findings and we conclude that there is significant hepatic uptake of this neuromuscular blocker in animals with normal liver function. The importance of the liver was further confirmed by the fact that, in all animals, it was necessary to increase the infusion rate of pipecuronium significantly during the first 1 h after reperfusion of the liver graft. However, dose requirement of pipecuronium was significantly less than that before crossclamping of hepatic vessels, probably because of decreased metabolic function of the hepatic graft immediately after transplantation [16]. The reperfusion of the liver graft was followed immediately by a transient decrease in arterial pH, which could also result in a larger dose requirement of pipecuronium. However, the change observed was probably not related to pH, as changes in the dose requirement of pipecuronium occurred after correcting the metabolic acidosis.

In contrast with our findings, Agoston and colleagues reported that, in cats, temporary hepatic exclusion did not alter significantly the intensity and the time-course of the neuromuscular blocking effects of pipecuronium [17]. However, these authors did not measure plasma concentrations of pipecuronium before and during a brief period of portocaval shunting (10 min). It is possible therefore, that changes in the pharmacokinetics of pipecuronium induced by the short exclusion of the liver are not reflected in neuromuscular effects. There may also be species-related differences in hepatic uptake and excretion of pipecuronium, as reported by the same research group for pigs and cats in hepatic uptake of other myoneural blockers [16, 18]. Previous studies have also suggested that there are differences in hepatic uptake and distribution of neuromuscular blocking drugs between the cat and humans [19, 20]. As pig and human liver have similar enzyme systems [21], the pig is probably more representative than the cat for studying the influence of the liver on the neuromuscular effects of muscle relaxants.

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THE ROLE OF α_1-ADRENOCEPTORS IN ADRENALINE-INDUCED HYPERKALAEMIA

H. ENSINGER, B. DIRKS, K. H. ALTEMEYER AND A. GRÜNERT

SUMMARY

The hyperkalaemic action of adrenaline was investigated in 44 anaesthetized domestic pigs. Plasma and epicardial concentrations of K^+ *were measured, in the latter case with an ion-selective electrode. Adrenaline 10 µg kg*$^{-1}$ *caused a rapid increase in the plasma concentration of* K^+ *from 4.2 to 5.9 mmol litre*$^{-1}$*. The magnitude and the time course of epicardial concentration of* K^+ *were similar. Alpha-adrenoceptor block with either phentolamine 5 mg kg*$^{-1}$ *(non-selective block) or prazosin 0.1 mg kg*$^{-1}$ *(selective* α_1*-adrenoceptor block) abolished the hyperkalaemic effect of adrenaline in the plasma and on the epicardium. The* α_1*-adrenoceptor agonist phenylephrine increased the* K^+ *concentration, but the* α_2*-adrenoceptor agonist UK 14.304 did not cause any change in concentration. These results suggest that the hyperkalaemia induced by adrenaline occurs in the interstitial fluid of the myocardium and is mediated by* α_1*-adrenoceptors. These findings may be important in patients at risk of hyperkalaemia, with implications, for example, in the use of suxamethonium during induction of anaesthesia.*

KEY WORDS
Complications: hyperkalaemia. Ions: potassium. Sympathetic nervous system: adrenaline, α-adrenergic antagonists

Sympathetic nerve activity has been shown to play a role in the external homeostasis of K^+. Beta-adrenoceptor block [1] or α-adrenoceptor stimulation [2] is known to impair extrarenal deposition of infused K^+ in humans and to attenuate the increased plasma K^+ associated with physical exercise [3]. Adrenergic mechanisms also cause a rapid biphasic change in the plasma concentration of K^+ [4].

Rapid changes in the myocardial concentration of K^+ may be one reason for electrophysiological disturbances [5]. Such changes may occur in patients whose sympathetic nervous systems are activated, for example by painful surgical procedures, tracheal intubation, hypercapnia or hypoxia or after injection of adrenaline. Administration of suxamethonium increases the plasma concentration of K^+ [6] and K^+ deposition may be disturbed in patients with α-adrenoceptor stimulation or β-adrenoceptor block. We therefore investigated the effects of adrenaline on plasma K^+ and on the epicardium with a K^+-selective electrode [7], as an index of myocardial K^+.

METHODS

Animal preparation

Approval from the Federal Government was given for the study. Domestic pigs (28–30 kg) were premedicated with azaperone 100 mg and atropine 2.5 mg i.m. and anaesthetized with metomidate 100 mg i.v. The trachea was intubated, and positive pressure ventilation commenced with 60% nitrous oxide in oxygen using a Siemens Servo 900 ventilator and adjusted to achieve normoxia and normocapnia. After tracheal intubation, the animals were given metomidate 150 mg, buprenorphine 0.6 mg and alcuronium 5 mg i.v. Anaesthesia was maintained with a continuous infusion of metomidate 3 mg min^{-1} and alcuronium 0.04 mg min^{-1}. Ringer's lactate solution was infused at a rate of 120 ml h^{-1}. The right and left femoral arteries and the left

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femoral vein were cannulated. Rectal temperature was maintained at 38 °C with a heating pad. Sternotomy was performed and the pericardium opened. The K^+-selective electrode was attached to the epicardium near the apex. After preparation the pig was placed in a Faraday cage and allowed to stabilize for 15 min.

Measurements and chemical analysis

K^+-selective electrodes were constructed and calibrated by the method of Hirche and colleagues [7]. Arterial pressure was recorded via the left femoral artery and heart rate derived from the ECG. The amplified output of the K^+-selective electrode was registered on a chart recorder. Blood samples for chemical analysis were centrifuged and the supernatant analysed for Na^+ and K^+ with a flame photometer (Beckman).

Experimental programme

Eight differently treated groups were studied: a control group and animals given adrenaline, phentolamine, phentolamine plus adrenaline, prazosin, prazosin plus adrenaline, phenylephrine and a selective α_2-adrenoceptor agonist, UK 14.304 (5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline) [8].

To verify the *in vivo* function of the K^+-selective electrode, a bolus of 5-mmol potassium chloride (1 mmol ml^{-1}) was injected. Before and 45 s after the injection, blood samples were taken and the increase in plasma and epicardial concentrations of K^+ measured. Another 15 min elapsed until the start of the experiment. When phentolamine or prazosin was used for receptor-subtype classification, these drugs were administered during the 15 min before the experiment, together with 6 % hydroxyethyl starch 300 ml. A blood sample to determine Na^+, K^+, pH, $P\mathrm{CO_2}$ and $P\mathrm{O_2}$ was taken (time $t = 0$ min). A bolus of adrenaline 10 $\mu g\,kg^{-1}$, phenylephrine 100 $\mu g\,kg^{-1}$, UK 14.304 3 $\mu g\,kg^{-1}$ or an equal volume of saline (3 ml) was injected during a period of 30 s. At $t = 1, 2, 4$ and 8 min after completion of the injection, blood samples were taken to determine Na^+, K^+ and, at $t = 8$ min, pH, $P\mathrm{CO_2}$ and $P\mathrm{O_2}$ also. As the experiments with UK 14.304 were carried out 1 year after the experiments with adrenaline, we measured only the plasma concentration of K^+. In preliminary experiments it was shown that UK 14.304 reached the maximum pressure effect without decreasing heart rate at a dose of 3 $\mu g\,kg^{-1}$.

Statistical analysis

Analysis of variance was performed for the statistical treatment of the data using the SAS program [9]. Results are expressed as means and SEM. $P < 0.05$ was taken as significant. If the analysis of variance showed a significant difference (treatment used as independent variable) t statistics modified by the Bonferroni method were calculated by comparing each treated group with the control group.

RESULTS

In vivo *function of the ion-selective electrode*

Baseline plasma and epicardial concentrations of K^+ in the control experiments were both 4.0 (0.2) mmol ($n = 8$). The injection of potassium chloride 5 mmol increased the plasma concentration of K^+ to 5.1 (0.2) mmol and the epicardial concentration to 5.3 (0.4) mmol ($n = 8$). Heart rate and mean arterial pressure were not affected by the injection of potassium.

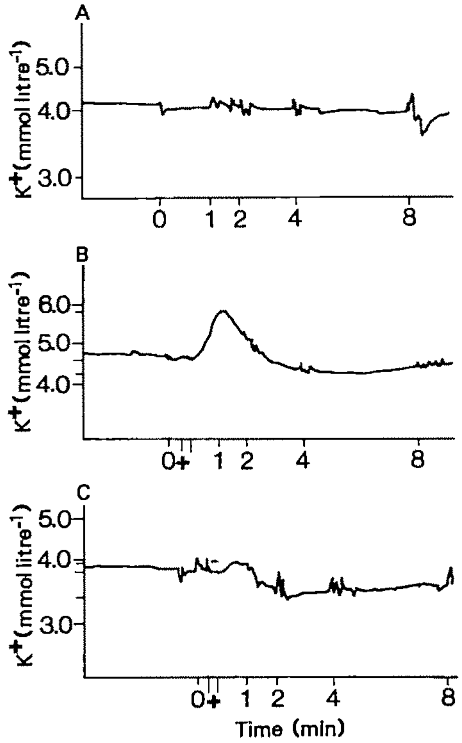

FIG. 1. Typical recordings from the potassium selective electrode. A: A control experiment; the withdrawal of blood caused artefacts at $t = 0, 1, 2, 4$ and 8 min. B: Adrenaline. C: Prazosin plus adrenaline.

Typical tracings of the output of the ion-selective electrode from three experiments (control, adrenaline, prazosin plus adrenaline) are shown in figure 1. In the control experiment, the epicardial concentration of K^+ remained constant. After injection of adrenaline, there was an increase in the epicardial concentration, followed by a decrease to less than the original value. In the experiment with the antagonist, only the decrease was detected.

Control studies

At $t = 0$ min, plasma concentration of Na^+ was 142 (1) mmol litre^{-1}, pH was 7.45 (0.02), P_{CO_2} 4.8 (0.15) kPa and P_{O_2} 18.8 (1.2) kPa ($n = 8$). Both plasma and epicardial concentrations of K^+ were 4.2 (0.2) mmol litre^{-1} at $t = 0$ min. These parameters remained constant at $t = 1, 2, 4$ and 8 min after the injection of saline 3 ml. Comparison of all groups did not show any difference for any of the parameters determined at $t = 0$ min.

Adrenaline

The absolute values for plasma and epicardial concentrations of K^+ are shown in tables I and II. The maximal effect in the plasma concentration of K^+ was reached after 1 min. The time course was similar in the epicardium, but the rapid decrease in K^+ concentration did not begin until 2 min after the injection of adrenaline.

Adrenaline increased mean arterial pressure from 64 (3) to 122 (5) mm Hg and heart rate from 120 (8) to 229 (10) beat min^{-1}.

Alpha-adrenoceptor block

Phentolamine 5 mg kg^{-1} and prazosin 0.1 mg kg^{-1} affected neither the basal values at $t = 0$ min nor the plasma or the epicardial concentrations of K^+ at $t = 1$, 2, 4 and 8 min (tables I, II). Both drugs abolished the increases in plasma and epicardial concentrations of K^+ caused by adrenaline and completely antagonized the in-

TABLE I. *Mean (SEM) plasma concentrations of K^+ before ($t = 0$) and at 1, 2, 4 and 8 min after administration of the study drugs.* *$P < 0.05$ *compared with* $t = 0$

		Time (min)				
Study drug	*n*	0	1	2	4	8
Control	8	4.2 (0.2)	4.2 (0.2)	4.2 (0.2)	4.2 (0.2)	4.2 (0.2)
Adrenaline 10 μg kg^{-1}	13	4.2 (0.2)	5.9 (0.3)*	4.6 (0.2)	3.8 (0.2)	4.0 (0.1)
Phentolamine 5 mg kg^{-1}	4	4.3 (0.3)	4.3 (0.3)	4.3 (0.3)	4.4 (0.3)	4.4 (0.3)
Phentolamine 5 mg kg^{-1} + adrenaline 10 μg kg^{-1}	5	3.8 (0.2)	4.0 (0.1)	3.8 (0.1)	4.1 (0.3)	3.9 (0.3)
Prazosin 0.1 mg kg^{-1}	4	4.4 (0.2)	4.4 (0.2)	4.3 (0.1)	4.4 (0.2)	4.3 (0.1)
Prazosin 0.1 mg kg^{-1} + adrenaline 10 μg kg^{-1}	5	4.3 (0.2)	4.4 (0.2)	4.0 (0.1)	3.9 (0.1)	4.1 (0.2)
Phenylephrine 100 μg kg^{-1}	5	4.1 (0.1)	4.7 (0.4)	4.2 (0.3)	3.9 (0.1)	4.0 (0.2)
UK 14.304 3 μg kg^{-1}	5	4.0 (0.1)	4.1 (0.1)	4.1 (0.1)	4.0 (0.1)	4.1 (0.1)

TABLE II. *Mean (SEM) epicardial concentrations of K^+ before ($t = 0$) and at 1, 2, 4 and 8 min after administration of the study drugs.* *$P < 0.05$ *compared with* $t = 0$

		Time (min)				
Study drug	*n*	0	1	2	4	8
Control	8	4.2 (0.2)	4.2 (0.2)	4.2 (0.2)	4.2 (0.2)	4.3 (0.2)
Adrenaline 10 μg kg^{-1}	13	4.2 (0.2)	5.9 (0.5)*	5.6 (0.4)*	4.1 (0.2)	3.8 (0.2)
Phentolamine 5 mg kg^{-1}	4	4.3 (0.3)	4.2 (0.3)	4.3 (0.4)	4.4 (0.3)	4.5 (0.8)
Phentolamine 5 mg kg^{-1} + adrenaline 10 μg kg^{-1}	5	3.8 (0.2)	4.1 (0.1)	3.7 (0.2)	3.6 (0.2)	3.8 (0.2)
Prazosin 0.1 mg kg^{-1}	4	4.4 (0.2)	4.2 (0.2)	4.2 (0.2)	4.5 (0.3)	4.3 (0.2)
Prazosin 0.1 mg kg^{-1} + adrenaline 10 μg kg^{-1}	5	4.3 (0.2)	4.7 (0.3)	4.3 (0.3)	4.2 (0.3)	4.3 (0.2)
Phenylephrine 100 μg kg^{-1}	5	4.1 (0.1)	5.7 (0.9)	6.1 (1.3)*	4.0 (0.1)	3.9 (0.2)

crease in arterial pressure without affecting the adrenaline-induced tachycardia.

Alpha-adrenoceptor activation

Phenylephrine 100 μg kg^{-1} increased the plasma concentration of K^+ (not significantly) and the epicardial concentration. Arterial pressure increased to a greater value with phenylephrine than with adrenaline, and the increase persisted for longer.

With UK 14.304 3 μg kg^{-1} min^{-1}, there was no change in the plasma concentration of K^+ (tables I, II).

DISCUSSION

In our experimental model, adrenaline caused an increase in the plasma concentration of K^+ followed by a short-term decrease. Time course and extent of the change were similar in plasma and epicardium. Treatment of the pigs with phentolamine 5 mg kg^{-1} abolished the hyperkalaemic and the pressor effect of adrenaline. As phentolamine has no β-adrenoceptor blocking properties, the receptor causing the hyperkalaemia is an α-adrenoceptor. For receptor subtype classification, experiments with the α_1-adrenoceptor antagonist prazosin were carried out [10]. A low dose of prazosin 0.1 mg kg^{-1} abolished the pressor response and the adrenaline-induced hyperkalaemia. These results suggest that adrenaline causes the hyperkalaemia by stimulation of α_1-adrenoceptors. The organ most likely to release K^+ upon adrenergic stimulation is the liver [11]. In an *in vitro* preparation of guineapig hepatocytes, prazosin blocked the K^+ efflux evoked by adrenaline [12]. In contrast, the preferential α_2-adrenoceptor antagonist yohimbine [13] only partially antagonized the efflux.

Phenylephrine is a selective α_1-adrenoceptor agonist [14]. The increase in the plasma concentration of K^+ evoked by phenylephrine was only about 50% of the increase seen after adrenaline. This finding is confirmed by previous observations [15, 16]. Only a combination of α- and β-adrenoceptor stimulation caused a similar increase in the plasma concentration of K^+ [15]. The explanation for this phenomenon may be a decrease in the hepatic blood flow by α-adrenoceptor stimulation [17] and hence a delayed washout of K^+ from the liver. The more pronounced increase in the K^+ concentration on the epicardium may be caused by relative hypoxia of the myocardium, where the oxygen supply is reduced by coronary artery constriction induced by phenylephrine [18] and the oxygen demand of the heart is increased by the increased afterload.

UK 14.304 is a selective α_2-adrenoceptor agonist [8]. The absence of any increase in the K^+ concentration after UK 14.304 further strengthens the concept that the hyperkalaemia found after injection of adrenaline is caused by α_1-adrenoceptor stimulation.

K^+-selective electrodes have been used *in vivo* to determine the K^+ concentration in the plasma and on the epicardium [7]. The epicardial concentration of K^+ was taken as an index for the K^+ concentration of the interstitial fluid of the myocardium. Downey [19] showed that under steady state conditions there is no difference between the K^+ concentration in the coronary sinus blood and in the coronary lymph, which is the drainage fluid of the extracellular compartment of the myocardium. Hirche [7] reported that after an i.v. injection of K^+, the time course and the amplitude of the K^+ fluctuation are similar, both in the coronary sinus blood and on the epicardium.

Hyper- and hypokalaemia are thought to be adverse conditions for general anaesthesia. As the major side effects are disorders of heart rhythm and conduction, the K^+ concentration of the myocardial extracellular fluid is of interest. Our experiments show that, after i.v. injection of K^+ or the administration of α-adrenoceptor agonists, there is an increase in the K^+ concentration of the myocardial extracellular fluid.

An increase in the plasma concentration of K^+ of 1.9 mmol $litre^{-1}$ is usually without effect or only causes minor acceleration of cardiac conductance. However, if the plasma concentration of K^+ is at the upper limit of or slightly above the physiological range, profound and rapid depression of conduction may occur with a 2-mmol $litre^{-1}$ increase in K^+ concentration [20]. The α-adrenergic mechanisms leading to hyperkalaemia may be important under conditions in which other mechanisms cause increases in K^+ concentration and in which the sympathetic nervous system is activated, especially in the presence of β-adrenoceptor block. In anaesthetized dogs, suxamethonium 1 mg kg^{-1} caused hyperkalaemia, prolonged and intensified by β-adrenoceptor block [21]. Another study [22] failed to confirm these results. β-adrenoceptor block had only a minor effect.

There are no reports on any adverse effects of hyperkalaemia in patients with β-adrenoceptor block. Cardiac arrhythmias during administration of suxamethonium are thought to be the result of the stimulation of vagal and sympathetic ganglia. However, the rapidly occurring changes in plasma concentration of K^+ caused by adrenergic stimulation have not been investigated in patients during induction of anaesthesia using depolarizing neuromuscular blocking drugs.

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USE OF THE CALCIUM AGONIST BAY K 8644 FOR *IN VITRO* DIAGNOSIS OF SUSCEPTIBILITY TO MALIGNANT HYPERTHERMIA

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SUMMARY

We have studied the effects of the calcium agonist BAY K 8644 on the in vitro *halothane test in 10 malignant hyperthermia-susceptible (MHS), 12 MH "equivocal" to halothane (MHEh), 30 MH non-susceptible (MHN) and 10 control patients. BAY K 8644 potentiated the halothane-induced contracture in muscle strips from both MHS and MHEh patients. The drug produced a more obvious difference in contracture responses between the MHEh group compared with the MHN and control groups.*

KEY WORDS

Hyperthermia: malignant, in vitro *test. Pharmacology: calcium channel blocker, BAY K 8644*

The halothane [1] and caffeine [2] contracture tests are the most reliable and specific indicators of malignant hyperthermia (MH) susceptibility [3, 4]. The European MH group [4] defined three categories of results for *in vitro* diagnosis: MH susceptible (MHS), normal (MHN) or MH equivocal (MHE) to either caffeine (MHEc) or halothane (MHEh). For the "equivocal" group, the *in vitro* results are inconclusive. In our experience, and that of others [3, 5–7], the halothane test appears to be the most reliable diagnostic test for MH susceptibility as more patients have an abnormal response to halothane than to caffeine. However, many of our MHEh patients do not develop a vigorous contracture to halothane and this causes difficulty in classification. The aim of this study was to examine the effects of BAY K 8644 in association with halothane on muscle bundles from the three categories of patients classified by the European MH Group. The agonist BAY K 8644 is structurally similar to dihydropyridine antagonists, but exerts opposite effects; it acts by stabilizing slow calcium channels in mode 2 (prolonged channel opening), thus greatly enhancing calcium influx [8, 9].

PATIENTS AND METHODS

We studied 52 patients presenting for diagnostic muscle biopsy as part of investigation for MH. None was taking drugs which might have influenced muscle contractility. Muscle biopsies were taken from the vastus lateralis muscle under combined block with lignocaine of the femoral nerve and lateral cutaneous nerve of the thigh. Biopsies were obtained also from 10 control patients with no personal or family history of MH, undergoing elective orthopaedic surgery. All muscle biopsies in the control patients were obtained from the quadriceps muscle. The control patients were apparently normal with regard to muscle function, in particular with respect to preoperative muscle atrophy induced by bed rest. The study was approved by the Lille University Studies Ethics Committee and informed consent was obtained from all patients.

For the *in vitro* test, muscle strips (approximately 15–20 mm in length with a diameter of

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2–3 mm) were carefully dissected. One end was pinned to the silicone bottom of the tissue bath which was perfused continuously (4–5 ml min^{-1}) with Krebs–Ringer solution at 37 °C and bubbled with preheated 5% carbon dioxide in oxygen. The other end of the strip was attached by a thin silk thread to a force transducer (Bioscience dynamometer UFI and biological amplifier 120). Preparations were stimulated directly via silver electrodes by rectangular current pulses of 2 ms duration and at twice the threshold intensity delivered at a frequency of 0.2 Hz by a stimulator (CEA-DAM model GPI-GE2198). The preparation was stretched until the amplitude of muscle twitch could not be increased further and was then allowed to stabilize during 15 min of isometric relaxation. Baseline and twitch tension were recorded continuously at low speed on a C1013 Siemens polygraph. Halothane was mixed with carbon dioxide in oxygen by means of a calibrated vaporizer (Fluotec Mark III) in concentrations of 0.5, 1, 1.5, 2 and 3 vol% as measured by gas chromatography corresponding to 0.097 ± 0.011, 0.204 ± 0.018, 0.364 ± 0.026, 0.534 ± 0.02 and 0.691 ± 0.072 mmol $litre^{-1}$, respectively. Both static and dynamic halothane contracture tests were performed as described previously [7, 10]. Caffeine was added to the Krebs–Ringer solution in increasing concentrations of 0.5, 1, 1.5, 2, 3, 4, 8, 16 and 32 mmol $litre^{-1}$. Two caffeine tests were performed also. For both halothane and caffeine procedures, the test giving the greatest contracture was used to make a diagnosis.

Diagnosis of susceptibility to MH. All patients were investigated according to the European MH protocol [4]. The criterion for MH susceptibility (MHS) was an increase in resting tension of at least 0.20 g at 2 vol% of halothane or less and at caffeine 2 mmol $litre^{-1}$ or less. Patients were classified MH equivocal (MHE) if one test was negative and the other was positive, and MH negative (MHN), if both tests were negative. All patients were tested against both halothane and caffeine, using separate muscle strips.

Experimental procedure. Using muscle strips obtained from the same biopsies, BAY K 8644 10 μmol $litre^{-1}$ was added to the Krebs solution 10 min before administration of halothane according to the same procedure as the static contracture test. BAY K 8644 solution was protected from light during the experiments.

Differences between the means of the groups for maximum contracture response to each concentration of halothane were analysed using Student's *t* test for independent samples. A P value < 0.05 was taken as significant.

RESULTS

Ten patients were diagnosed as MHS, 12 as MHEh and 30 as MHN. All the control patients had normal contracture responses to halothane and to caffeine. None of the patients was found to be equivocal to caffeine (MHEc). Indications for investigation of the 62 patients and their classification based on the results of the *in vitro* tests (fig. 1) are shown in table I.

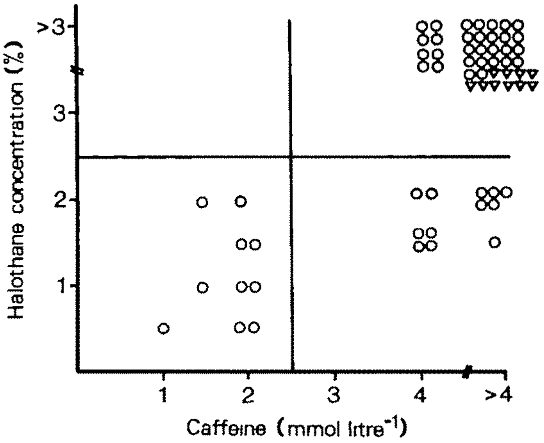

FIG. 1. Diagram by the European MH group. Threshold concentration for each patient to halothane and caffeine. ○ = Patients investigated for MH; ▽ = controls.

TABLE I. *Reasons for investigation and results of* in vitro *tests in 52 patients investigated for susceptibility to malignant hyperthermia and 10 control patients*

	MHS	MHN	MHE	Total
Relative of MHS proband	10	19	7	36
Possible MH reaction		2		2
Others				
Neuroleptic malignant syndrome		2		2
Heat stroke		1		1
Duchenne muscular dystrophy		1	1	2
Non-specific myopathy		5	4	9
Control		10		10
Totals	10	40	12	62

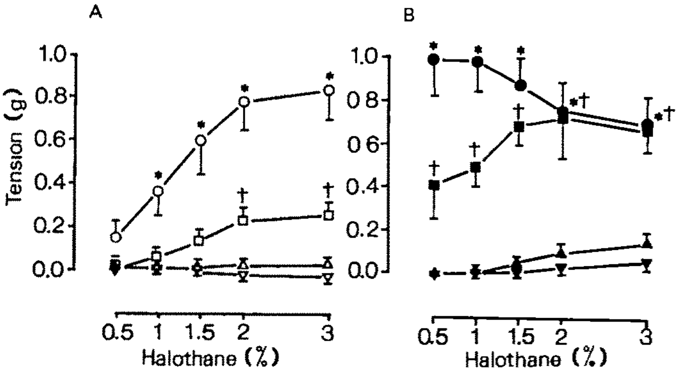

FIG. 2. Effects of BAY K 8644 on the response to halothane in diagnostic muscle biopsies from MHS, MHEh, MHN and control patients. A: Halothane dose-response curves in the absence of BAY K 8644. ○ = MHS ($n = 10$); □ = MHEh ($n = 12$); △ = MHN ($n = 30$); ▽ = control ($n = 10$). B: Halothane dose-response curves in the presence of BAY K 8644. ● = MHS ($n = 10$); ■ = MHEh ($n = 12$); ▲ = MHN ($n = 30$); ▼ = control ($n = 10$). $P < 0.05$: *MHS compared with MHN and control; †MHEh compared with MHN and control.

The muscle responses (means (SEM)) of the MHS, MHEh, MHN and control groups to increasing concentrations of halothane are expressed graphically in figure 2. No increase in resting tension was observed in the MHN and the control group, whereas concentration-dependent contractures developed in the MHS group ($P > 0.05$) with 1, 1.5, 2 and 3 % halothane (fig. 2A). In the MHEh group, the halothane contracture was significant only with 2 and 3 % halothane. In 11 of the 12 MHEh patients, the halothane threshold concentration (the minimal concentration of halothane eliciting a sustained increase in tension of 0.2 g) was 2 %. With 2 % halothane, the contracture was 0.23 (0.03) g in the MHEh group and 0.77 (0.17) g in the MHS group.

Preincubation for 10 min with BAY K 8644 10 μmol litre^{-1} significantly enhanced the halothane contracture in both the MHS and MHEh groups (fig. 2B). The contracture was significant at all halothane concentrations in the two groups and the effect was marked particularly with the smallest concentration of halothane. In the MHS group, the muscle strips developed a contracture of 1.01 (0.17) g as soon as (0.5 %) halothane was added to the carbon dioxide in oxygen. This was observed in 10 muscle bundles from the 10 MHS patients. In this MHS group, the addition of BAY K 8644 was associated with a decrease in tension as the halothane concentration increased. When 2 % halothane was given, there was no difference between the tension developed in the presence or absence of BAY K 8644. In the MHEh group, the muscle strips developed a contracture of 0.44 (0.15) g with 0.5 % halothane.

As population averages are of little value in deciding if an individual patient belongs to the MHN group, data are presented in graphic form (fig. 3), which may clarify the range of values separating obvious normal from abnormal results. MHS muscle strips developed consistently a contracture of at least 0.20 g with 0.5 % halothane and MHEh muscle strips developed the same

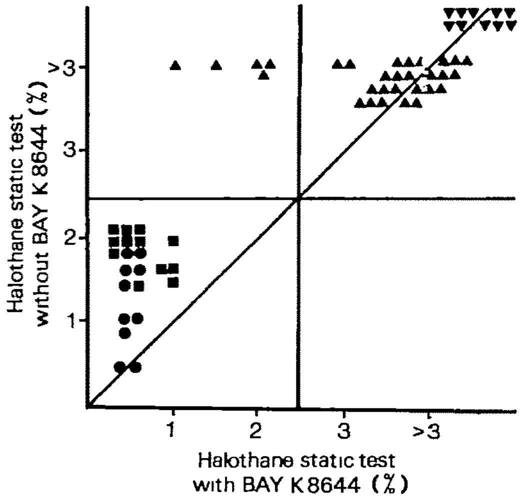

FIG. 3. Relationship between halothane test in the presence or in the absence of BAY K 8644 in 62 patients. See figure 2 for means, SEM and statistical analysis. ● = MH susceptible (MHS); ■ = MH equivocal to halothane (MHEh); ▲ = MH non-susceptible (MHN); ▼ = control.

level of contracture with 1% halothane or less. No contracture was seen for the control patients and for all but one of the MHN patients with 1% halothane.

DISCUSSION

This study indicates that BAY K 8644 potentiated the halothane-induced contracture in skeletal muscle from both MHS and MHEh patients. This action was marked particularly with the smallest concentration of halothane for the MHS group. The very high sensitivity (contracture) of these MHS muscle bundles rapidly induced muscle fatigue which could explain the paradoxical decrease in tension observed when halothane concentration increased. Furthermore, in the presence of BAY K 8644, the halothane test induced a greater difference in contracture responses between the MHEh group on one hand and the MHN and the control group on the other.

In our study, five of the 12 MHEh patients were patients with neuromuscular disease. Muscle strips from these patients behaved in the same manner as MHEh muscle from relatives of MHS probands. Our results with myopathic muscle may not necessarily be equated with clinical susceptibility to MH. However, other studies performed with the halothane contracture test [11] or the caffeine skinned fibre test [12] have also shown an augmented response in several neuromuscular disorders. Hence, these previous reports, together with the present findings, may suggest that this population is at higher risk for MH than the general population.

Some authors have suggested that the use of other tests in addition to the classical halothane–caffeine test improves the reliability of diagnosis. Tests involving simultaneous exposure to both halothane and caffeine produce data which overlap between normal and known MHS patients [3]. Takagi and colleagues [12] have suggested the use of a single skinned muscle fibre test which seems to correlate with the muscle bundle test [13]. However, this method is difficult to perform and time consuming. Furthermore, the slightest contamination of distilled water with calcium invalidates the test.

The action of BAY K 8644 on MH susceptible muscle in the presence of halothane is not unexpected. In MH muscle, intramyoplasmic calcium increases with the application of halothane and this change correlates well with the magnitude of developed contracture. The source of this increased intramyoplasmic calcium is thought to be either sarcoplasmic reticulum [14, 15] or sarcolemma [16]. The addition of BAY K 8644 to MH muscle provides an extracellular source of calcium and enhances the effects of halothane.

The fact that the tests in the MHEh group became more similar to those in the MHS group with the combination of BAY K 8644 and halothane suggests that the combined test may allow more accurate diagnosis in equivocal patients. The MHE population was not affected by the combined test. We conclude that the use of BAY K 8644 may help to establish more definite end-points for normal and abnormal responses to halothane tests.

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EFFECTS OF HALOTHANE, ENFLURANE AND ISOFLURANE ANAESTHESIA ON RENAL PLASMA FLOW

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SUMMARY

Effective renal plasma flow (ERPF) and linear cardiac output (aortic blood velocity) were measured in 15 patients who received halothane, enflurane or isoflurane in oxygen. All three agents caused a significant reduction in ERPF ($P < 0.05$) and the effect was greater at 1.25 MAC than at 0.75 MAC. No significant difference was demonstrated between the agents. Linear cardiac output did not change significantly during the study, suggesting that the observed reduction in ERPF was not caused by cardiovascular depression.

KEY WORDS

Anaesthetics, volatile: enflurane, halothane, isoflurane Heart: aortic blood velocity Kidney renal plasma flow.

Although the effects of halothane, enflurane and isoflurane on renal function, and particularly on renal blood flow, have been studied elsewhere [1–3], agents were examined individually, during separate experiments, by separate researchers. Hence, it is difficult to compare data. Furthermore, there were drawbacks in methodology in previous trials, but these may now be circumvented by recent advances. For example, an assessment of fractional distribution of cardiac output to the kidney could not be made, as cardiac output had not been measured, probably because no reliable non-invasive method of measuring cardiac output was available. Lastly, standard renal clearance techniques used to measure renal blood flow become inaccurate during low or changing urine output, conditions often encountered during anaesthesia [4, 5]. To overcome this problem, fluid loads and ethyl alcohol were administered to promote diuresis, but these manoeuvres would have altered measured flows. Newer developments now permit some of these difficulties to be overcome [6–11].

PATIENTS AND METHODS

Approval for the study was obtained from the Joint Ethics Committee of the University of Wales College of Medicine and South Glamorgan Health Authority.

Fifteen adult patients undergoing general or ear, nose and throat surgery, gave informed written consent to the trial. They were aged 25–50 yr, and ASA grade I or II. Patients with evidence of cardiovascular or renal disease or receiving intercurrent drug therapy were excluded.

Preanaesthetic medication consisted of lorazepam 2 mg orally 2 h before transfer to the operating theatre. Under local anaesthesia, a 17-gauge i.v. cannula was inserted in one forearm for fluid infusion and administration of radioisotopes, and a 14-gauge cannula in the antecubital fossa of the opposite arm for blood sampling and the administration of anaesthetic drugs.

Before measurements were made, patients were rehydrated with 4% dextrose and 0.18% saline at 10 ml/kg body weight over a period of 40 min (as all were investigated before afternoon surgery after only a light breakfast at 06:00). Electrocardiogram and indirect arterial pressure monitoring was commenced and recorded at 5-min intervals. Then, effective renal plasma flow

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(ERPF) was measured using a non-invasive radioisotope method with three isotopes: iodine-123, -125 and -131 [11]. As a measure of cardiac output, mean blood velocity in the ascending aorta was measured using an ultrasonic pulsed Doppler transcutaneous aortovelograph, with the probe placed in the suprasternal notch [6–9].

Anaesthesia was induced with etomidate 0.2–0.3 mg kg^{-1}, followed by suxamethonium 1 mg kg^{-1} i.v. The larynx was sprayed with 4% lignocaine and the trachea intubated. Anaesthesia was maintained with halothane, enflurane or isoflurane in oxygen to achieve an end-tidal vapour concentration of 0.75 MAC. The choice of anaesthetic vapour was made according to a randomized programme to produce three groups each of five patients. The gas mixture was delivered via a non-rebreathing system (Manley Pulmovent ventilator) set for a minute volume at approximately 150 ml/kg body weight. End-tidal concentration of carbon dioxide was monitored (Datex Normocap) and maintained at 5% by adjusting tidal volume or adding carbon dioxide to the inspired mixture as necessary. End-tidal anaesthetic vapour concentration was monitored using a Datex Normac. MAC was adjusted for age in patients given halothane or isoflurane [12, 13]; proportionate adjustments were made for those anaesthetized with enflurane.

When an end-tidal vapour concentration of 0.75 MAC had been maintained for 15 min, aortovelography and measurement of ERPF were repeated. Inspired vapour concentration was increased until end-tidal vapour concentration was 1.25 MAC, and when this had been maintained for 15 min, aortovelography and ERPF measurements were repeated. At the conclusion of this third pair of measurements, the patient was taken into the operating room for surgery.

The output of the aortovelograph was analysed and stored using a BBC microcomputer. Mean linear cardiac output (aortic blood velocity representing cardiac output) was expressed as a percentage of the awake value. ERPF results were expressed in this way also, so that means for each group of five patients could be calculated. For each individual subject, the aortovelograph data were used to adjust the actual ERPF results to give "corrected" ERPF, an estimate of what ERPF would have been if cardiac output had not changed, so that any changes in fractional distribution of blood to the kidneys could be observed.

Halothane, enflurane and isoflurane groups were compared using unpaired *t* tests with Bonferroni correction. Comparisons between different levels of anaesthesia using the same vapour were made using paired *t* tests with Bonferroni correction. Values of $P < 0.05$ were considered significant.

RESULTS

Table I summarizes patient data. The actual renal plasma flow decreased significantly from awake values at both 0.75 MAC and 1.25 MAC for all agents tested, but there was no significant difference between the agents (table II). For this comparison the *t* test used would have a power of 0.87 in demonstrating a difference of 30%. The results found by previous workers are recorded for comparison (table II).

Changes in cardiac output are presented in table III.

TABLE I. *Age and weight of patients (mean (SD) for each group)*

Group	Age (yr)	Weight (kg)
Halothane	37.8 (7.5)	75.1 (15.4)
Enflurane	36.2 (5.6)	67.5 (8.6)
Isoflurane	37.2 (7.7)	70.9 (17.7)

TABLE II. *Mean (SEM) ERPF compared with depth of anaesthesia (MAC units) for halothane, enflurane and isoflurane groups, as percentage of awake value, in the present and previous studies*

	MAC value		
	0.75	1.25	Previous studies
Halothane	80 (6.6)	74 (3.1)	62 (at 2 MAC) [1]
Enflurane	77 (5.6)	70 (3.6)	77 (at 0.8 MAC) [3]
Isoflurane	77 (3.3)	70 (4.6)	51 (at 1 MAC) [2]

TABLE III. *Mean (SEM) changes in cardiac output (measured as mean aortic blood velocity) as percentage of awake value compared with depth of anaesthesia (MAC units) for halothane, enflurane and isoflurane groups*

	MAC value	
	0.75	1.25
Halothane	105 (9.8)	98 (9.1)
Enflurane	95 (5.6)	86 (7.7)
Isoflurane	105 (8.3)	100 (9.8)

TABLE IV. *ERPF "corrected" for cardiac output changes: means* (SEM) *for each group as percentage of awake value, compared with depth of anaesthesia* (*MAC units*)

	MAC value	
	0.75	1.25
Halothane	81 (13.9)	78 (10.3)
Enflurane	82 (5.9)	84 (7.28)
Isoflurane	75 (4.1)	71 (3.4)

Correcting the actual ERPF values for changes in cardiac output reduced the significance of the changes, although the group means are similar to the actual ERPF values (table IV). Isoflurane at 0.75 and 1.25 MAC and enflurane at 0.75 MAC caused significant depression in corrected ERPF. Mean arterial pressure decreased in all subjects after anaesthesia, and the maximum depression from the awake value, expressed as a mean for all 15 patients, was 9%. The maximum depression occurred usually during 1.25 MAC anaesthesia.

DISCUSSION

Many factors, independently or in concert, may cause a reduction in renal blood flow. In the investigation of anaesthetic agents the effect of other factors must be excluded as far as possible. Some previous studies did not exclude the effects of stress, anxiety, dehydration, premedication, surgical stimulation and artificially-induced diuresis. The present trial was designed to avoid or reduce the effects of these complicating factors as far as is compatible with clinical research.

The method used to measure ERPF is based on the plasma clearance of radiolabelled para-aminohippuric acid (PAH) [11], and assumes (as do all methods based on PAH clearance) that anaesthesia does not greatly alter the renal PAH extraction ratio. The possibility of such a change has not been explored widely, but Deutsch and colleagues showed in two volunteers that halothane did not alter PAH extraction ratio [1]. During times of low urine production, PAH may be stored in the kidney [5], but this would not affect calculation of PAH clearance based on plasma samples.

The study has shown significant depression of ERPF during anaesthesia with each of the three agents. The effect appears to be dose related, although the only further significant depression of ERPF after 0.75 MAC occurred with isoflurane. Previous studies also have shown that the renal effects of anaesthetic agents are dose related [14, 15]. Since conditions of positive pressure ventilation were the same at 0.75 and 1.25 MAC, the use of IPPV did not seem greatly to affect the results.

The depression of ERPF noted with halothane and enflurane was similar quantitatively to that observed in previous studies (table II), but that for isoflurane was not. Our data suggest little difference between the agents, whereas previous work indicated a more profound depression with isoflurane, although valid comparisons between agents should not be drawn too finely from previous studies for the reasons outlined above. However, it is interesting to note that in various previous studies, only subjects in an isoflurane trial [2] and not those in halothane and enflurane trials, were treated with extra i.v. fluid, reduction of depth of anaesthesia, or both, if they became hypotensive.

This study used mean aortic blood velocity as an indicator of cardiac output, based on two assumptions. The first is that the velocity profile of blood in the ascending aorta remains relatively constant whilst the velocity varies; spectral analysis suggests that this is so [16]. The second is that there is no significant change in the mean cross-sectional area of the aorta during the period of measurement. This is likely to be the case, as studies which make this assumption when comparing Doppler methods with, for instance, thermodilution, show good relationships [8].

In contrast, one study reported the relationship between intra-aortic pressure and aortic diameter [17], and showed that diameter decreased as mean pressure decreased, although to a variable degree in different patients. If this were the case, then velocity measurements would decrease proportionately less than corresponding decreases in flow (as aortic area would be reduced at the same time); in other words, Doppler measurements would underestimate any change in cardiac output. This might have contributed to the fact that we measured only small changes in linear cardiac output. However, in other circumstances, we and many other workers have measured large changes in linear cardiac output using this technique. Furthermore, whilst a reduction in cardiac output often follows induction of anaesthesia, some studies have reported no change or even an increase in cardiac output [18].

The Doppler instrument we used was built by the biomedical engineering department of the University Hospital of Wales, using the same principles as commercially available models. It was tested for accuracy *in vitro* on a flow rig before being used in clinical trials.

Aortic velocity figures were used to adjust ERPF data in each case, to simulate ERPF changes irrespective of change in cardiac output (table IV). The "corrected" ERPF changes look similar to the original ERPF changes, the main difference being that only three of the six group means differed significantly from control: those for isoflurane at 0.75 MAC and 1.25 MAC, and for enflurane at 0.75 MAC. The absence of statistical significance for the other three corrected means is a result of the larger SEM in these cases, induced by variance in the individual aortic blood flow measurements. Presumably analysis of larger groups in a study would rectify this.

Taken as a whole, the data show that the three anaesthetic vapours tested caused a significant decrease in ERPF, and that there was no difference between the agents in degree of depression caused. The depression seemed to be independent of any change in cardiac output, and in the absence of significant hypotension.

Renal blood flow is known to decrease during many types of anaesthesia, and the mechanism responsible is not understood. The fact that renal blood flow decreases during anaesthesia in spite of maintained perfusion pressures has led some to believe that autoregulation of renal blood flow is impaired. However, studies claim that halothane does not affect autoregulation [19]; and autoregulation has been shown to persist in isolated perfused kidney exposed to halothane [20]. Moreover, studies on the isolated dog kidney revealed that halothane acts as a direct renal vasodilator [21]. This evidence suggests that anaesthesia alters ERPF by an indirect effect on the kidney; evidence from experiments measuring tubular function concurs with this. Hollenberg summarized the situation thus: "It is equally important to recognise that the concept of autoregulation does not preclude quantitatively important changes in renal perfusion; rather, when such changes occur they are rarely due to changes in perfusion pressure unless striking hypotension is present. Thus, local and systemic vasoactive factors play a much more important role in determining renal perfusion and function" [22].

Some researchers propose that renal vascular resistance increases during anaesthesia, and some that it decreases. Various extrinsic systems have been implicated, including renin–angiotensin system activation, sympathetic nervous system activation, catecholamine release, and antidiuretic hormone release [1, 17, 23]. Activation of volume receptors caused by relative decrease in plasma volume may cause renin activation [24], although there is said to be complete tachyphylaxis to angiotensin in the renal vascular bed within 20 min [22]. Nevertheless, inhibition of the renin–angiotensin system in dogs prevents the decrease in renal blood flow and the increase in renal vascular resistance associated with barbiturate anaesthesia [25]; this might implicate the renin–angiotensin system as at least a partial cause of the observed effects.

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FACTOR ANALYSIS IN DIFFICULT TRACHEAL INTUBATION: LARYNGOSCOPY-INDUCED AIRWAY OBSTRUCTION

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SUMMARY

We have studied eight patients with a history of difficult tracheal intubation, using x-ray laryngoscopy and local anaesthesia, a curved Macintosh blade and a standard intubating position. The view obtained was better than recorded previously during general anaesthesia in two patients, and in a third the x-ray showed that positioning the blade tip beneath the epiglottis would have improved vision, suggesting that reproducibility of the assessment may not be consistent. The "ease of intubation" and "complementary" angles may be helpful in the assessment of such patients. A "peardrop" effect is described whereby during laryngoscopy, the epiglottis became pressed against the posterior pharyngeal wall as a result of tongue compression. In the absence of muscle paralysis, removal of the blade caused immediate correction. However, during anaesthesia with neuromuscular block it is suggested that this not only occurs more readily but, may not correct when the blade is removed. Iatrogenic airway obstruction during moderately difficult tracheal intubation may be common and should be anticipated.

KEY WORDS

Anatomy: cervical vertebrae, hyoid, mandible, larynx. Intubation, tracheal: complications.

We have proposed previously a standard intubating position to investigate patients presenting difficulties with tracheal intubation [1] and have shown that x-ray laryngoscopy is useful in demonstrating the relevance of soft tissue effects [2]. In normal volunteers, successful laryngoscopy with a curved laryngoscope blade depends largely on appropriate positioning of the tip of the blade so as to move the hyoid forward and elevate the epiglottis. In a preliminary report in which patients with a history of difficult laryngoscopy were studied [3], two mechanisms were suggested to be responsible for the difficulty. The blade tip could be positioned correctly with respect to the hyoid but forward movement constrained, for example by calcified stylohyoid ligaments. Alternatively, despite appropriate advancement of the blade tip, approximation to the hyoid may be prevented by the tongue. In both circumstances the usual mechanism for elevating the epiglottis is rendered ineffective and laryngeal exposure compromised. This paper reports further analysis of such patients.

PATIENTS AND METHODS

After local Ethics Committee approval, eight patients (three female; mean age 53 (SD 19) yr) with a recent (within 12 months before the study) history of difficulty with tracheal intubation consented to take part in the study. An anaesthetist of senior registrar or consultant status had decided originally that the patients presented difficulty at laryngoscopy. No patient was pregnant.

Physical characteristics were recorded, including dental impressions and mandibular translation (obtained by biting into dental wax). Neck length was measured as the vertical distance from the sternal notch to the middle of the external

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auditory meatus with the subject erect and the head in a neutral position. Neck circumference was the minimum value. Ramus length was the vertical distance from the condyle to the angle of the jaw. Maxilla and mandible lengths were the antero–posterior distances from the front of the upper incisors to the posterior border of the condyles, and the tip of the symphysis menti to the condyles, respectively.

The x-ray laryngoscopy technique and the subsequent analyses were as reported previously [4]. The laryngoscopy grading used was as follows: E0 = *severe*, no part of glottis seen; E1 = *moderate*, epiglottis seen, immobilized on pharyngeal wall; E2 = *intermediate*, epiglottis partly elevated, and no clear indication of glottic midline; E3 = *minimal*, epiglottis partly elevated, glottic midline position obvious (because interarytenoid groove obvious); E4 = *not difficult*, posterior commissure or cords seen.

For analysis of the x-rays, the points shown in figure 1 were used. As far as possible, the variables investigated were midline angles. The cervical spine was described as "bowed" if any of the upper cervical vertebrae protruded forward of a line at 35° (the standard neck flexion angle) to the front of C6. From our earlier study in normal volunteers, expected values for normal length ratios and angles were derived as shown in table I. Abnormality was described in terms of the appropriate 2 and 3 SD from the mean for the volunteers.

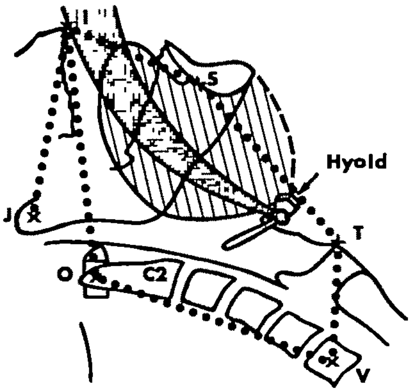

FIG. 1. Points for analysis of x-rays (joined by dotted lines): I = tip of upper incisors; O = central point of the anterior half of the vertebral foramen of atlas; V = central point on the body of C6; T = most anterior–inferior position of the airway behind the thyroid cartilage and above the vocal cords; S = mid-point on the inner surface of the mandibular symphysis (from the tip of the lower incisors to the lower border of the mandible); J = radiological mid-point between the centres of the two condyles. The diagram shows the expected position of the laryngoscope blade (stippled) relative to the tongue (cross-hatched). Note that the blade is completely around the tongue reaching to just behind the body of the hyoid. The main bulk of the tongue is pushed forward between the mandible and hyoid and the dashed line represents the anterior delineation of the tongue.

RESULTS

Table II summarizes the x-ray and clinical abnormalities. From the original descriptions, difficulty of intubation was equivalent to grade E1–E2 in each patient. At x-ray laryngoscopy the posterior commissure was seen in two patients. One was asthmatic and the previous anaesthetic had been complicated by bronchospasm during induction. Unilateral stylohyoid ligament calcification was present in the other patient and x-ray showed that rotation of the hyoid forward away from the immobilized side had revealed the larynx. Patient No. 6 was graded E2 at x-ray laryngoscopy, but an "eyeline" from the upper incisors tangential to the blade indicated that, had the blade been positioned behind the epiglottis, the glottic midline should have been seen (E3). The two patients with "short neck" indices had narrowing of C5 and C5 + C6 vertebrae, respectively, and the "bull neck" index was consistent with the clinical appearances.

The midline angles in figure 1 were determined from the x-rays. In the polygon VOIST, only the angles VOI and IST were different from those of normal subjects ($P < 0.01$ and $P < 0.002$, respectively). The spread of normal values suggested the difference was fortuitous in the case of angle VOI, but in the triangle IST, the angle SIT was not only different from the normal ($P < 0.001$), but also appeared to be a sensitive index of degree of difficulty (table II). For this reason it was called the "Ease of Intubation (EoI)" angle. The angle ITS was different also from normal ($P < 0.01$) and was considered an independent, "complementary" angle.

No significant difference in translation movements of the mandible was found compared with normal individuals. The "face line" and "tracheal alignments" [4] confirmed that approximation to the standard position was achieved in each patient.

"*Peardrop*" *phenomenon*

In all four cases of greatest difficulty in this study (E1 grade laryngoscopy) a mechanism (fig. 2) was apparent which suggests that airway

TABLE I. *Definitions for abnormality. Angular reference points as shown in figure 1; other measurements are described in the text. Height refers to overall body height. Values are 2 and 3 SD from the mean values in normal volunteers [4]. Asterisks are for purposes of reference in table II*

Character	Components	Defining angle/ratio	
		2 SD(*)	3 SD(**)
Bull neck	Height/neck circumference	<4.4	<4.1
Short neck	Height/neck length	>10	>11
Long ramus	Height/vertical height of ramus	<25	<21
Long maxilla	Height/effective length maxilla	<18	<16
Mandible/ maxilla	Relative lengths	<1.0	<0.9
Angle SIT	"Ease of intubation" angle (EoI)	<12°	<9°
Angle ITS	"Complementary" angle (Com)	<9°	<6°
Angle JIT	Condyle/incisor/trachea angle	>68°	>72°

TABLE II. *X-ray features, neck and jaw characteristics. Laryngoscopy gradings are defined in the text. SHC = Calcification of stylohyoid ligaments. In patient No. 7 the ramus extended beyond the film so JIT could not be measured. Abnormal indices are defined in table I (beyond the appropriate 2 SD (*) and 3 SD (**) limits)*

Patient No.	(M/F)	Grade	EoI°	Com°	X-ray features	Soft tissues	Jaw comment
1	F	E4	19.0	12 0	SHC—but hyoid could rotate forward	—	—
2	M	E1	3 5**	2.0**	—	Bull neck**	Long maxilla**; long ramus* Short mandible/maxilla* Large JIT*
3	M	E1	1.0**	0.5**	Narrowed C5 body	Short neck**	Large JIT**
4	M	E1	6 5**	5.0**	Hypertrophic anterior osteophytes, C3–C5	—	Symphysis hypertrophic (protruded inwards)
5	M	E4	16.5	13.5	—	—	—
6	F	E3	12*	10	Blade below epiglottis and arytenoids visible	—	—
7	M	E1	1 0**	0.5**	Narrowed C5 + C6 bodies	Short neck*	Long maxilla**; long ramus*
8	F	E2	10.5*	8.0**	SHC—immobilized hyoid. Vertebrae bowed forward	—	—

obstruction during laryngoscopy is almost inevitable in such patients. Compression of part of the tongue occurred, forcing the tip of the blade further posteriorly than might otherwise be expected.

Figure 2 shows that the tongue is in contact with the posterior pharyngeal wall and has its lower margins extending along the greater horns of the hyoid. Where the space for the tongue is limited, the laryngoscope blade inevitably encroaches upon it. The tongue is pushed into the pharynx and against the mandibular symphysis as the blade is advanced. When the handle is pulled forward, the limitations imposed by the symphysis result in further downward force on the tongue. The hyoid and thyroid cartilage limit downward movement and the trapped anterior tongue becomes moulded into a "peardrop" shape.

The forces within the tongue are transmitted in all directions at its lower part and as a result the epiglottis is pressed against the posterior pharyngeal wall. In effect, the anterior movement of the laryngoscope handle results in a backwards force exerted at the blade tip. This is in keeping with the clinical observation that under such circumstances it may be difficult to lift the epiglottis off the posterior pharyngeal wall, even with a bougie positioned directly beneath it.

Where the epiglottis is not fixed against the pharyngeal wall, an intermediate "partial peardrop" effect may be seen (fig. 3). Here the blade displaces the tongue, but not sufficiently to make contact with the hyoid, so the view is compromised. The backwards force on the epiglottis is less than with the complete peardrop effect. In the case represented in figure 3, the arytenoids

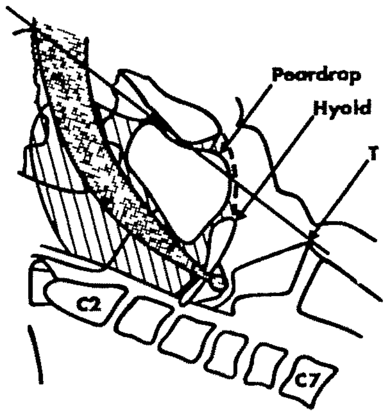

FIG. 2. The "peardrop" phenomenon. The laryngoscope blade tip is pressing against the epiglottis which is folded down against the posterior pharyngeal wall. A line is superimposed from the tip of the upper incisors (point I in figure 1) to the anterior airway point T. The blade tip is well back from the hyoid body. By comparison with figure 1, the tongue is relatively large and the area involved in the peardrop effect is shown unmarked.

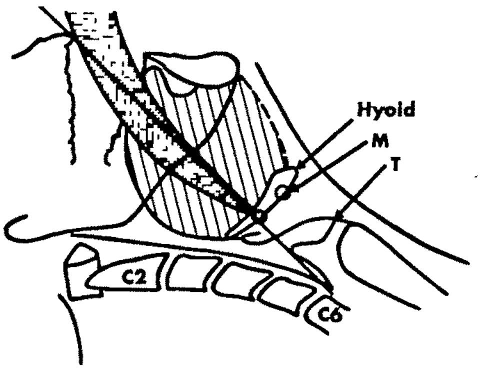

FIG. 3. "Partial peardrop" effect. The blade is not completely around the tongue. T is the anterior airway point as before, and M is an indication of where the blade tip might be expected to be located under normal circumstances. An eyeline is shown from the incisors along the under surface of the laryngoscope blade.

and larynx are shown displaced forward from the posterior pharyngeal wall. This implies that the laryngoscopic view depends on the degree of movement of the soft tissues, the actual position of the blade tip and the direction of application of the various forces involved. This intermediate stage was not seen in any of the present group of patients, so its further significance is discussed in the accompanying paper on patients with a history of difficult laryngoscopy during pregnancy [5].

DISCUSSION

The principal finding of this study is that the generally favoured curved laryngoscope blade is of limited usefulness in patients in whom laryngoscopy is of moderate difficulty and in certain circumstances may be in part responsible for some of the difficulty encountered. This observation could have important implications for future developments in laryngoscopy.

The "peardrop phenomenon" seen with x-ray laryngoscopy is caused by compression of the tongue and postero–inferior displacement results in airway obstruction on insertion of the laryngoscope. In awake, non-paralysed subjects the obstruction is corrected on removal of the laryngoscope. This suggests that local analgesia may be more appropriate in difficult cases as the tongue may be less liable to such effects when not paralysed. Under general anaesthesia with neuromuscular block it should not only occur more easily because of reduced muscle tone, but the obstruction is unlikely to clear on removal of the blade (as when assisting ventilation during a prolonged attempt at intubation).

Although the obvious action to deal with this problem is to pull the tongue forward again into the mouth, this may be difficult, for the reasons causing the problem with laryngoscopy (large tongue for the space available, limited mouth opening, or both). Other measures may also be affected. The introduction of a laryngeal mask, for example, might imitate the action of the laryngoscope blade and also tend to produce a "peardrop" effect itself. Where laryngoscopy precedes placement of such a mask, its effectiveness or otherwise may depend on whether or not the tongue remains mostly in the pharynx as a result of the laryngoscopy.

All the patients in this study were originally deemed difficult by an anaesthetist of at least senior registrar status. The finding of much better laryngoscopic vision during the investigation in two, and a suggestion that placing the blade below the epiglottis would have improved the view in a third subject, implies that reproducibility for this assessment should be questioned. It could be inferred that the inconsistency seen with senior practitioners would be worse when less experienced anaesthetists were involved. This must cast some doubt on the validity of studies aimed at predicting difficulty where there is no independent confirmation other than a single laryngoscopic assessment. In the present study, inconsistencies occurred only when there was a single documented laryngoscopy beforehand.

Perhaps one of the main limitations of assessment by laryngoscopy is its subjective nature, and hence it is proposed that the criteria defined in table I may be used as the basis for an "objective supplementary assessment". Cormack and Lehane [6] suggested that E0 grade laryngoscopy (epiglottis not seen) was unlikely to occur in the absence of obvious anatomical abnormality. The present work confirms this assertion, since all four E1 grade patients had multiple abnormalities when assessed by objective assessment criteria.

An objective assessment might be useful in a patient in whom difficulty with laryngoscopy is reported. The angular measurements require x-ray laryngoscopy under local anaesthesia, but the other measurements may be made with the minimum of equipment. The indices themselves were derived from only 10 normal volunteers and must be treated with caution at the present time. Certain problems associated with difficulty at laryngoscopy (such as limited mouth opening) were not encountered in this study. The list of assessments is obviously not exhaustive, but the principle that each index is independent of the others, takes relative size into account and is defined by the appropriate 2 and 3 SD from a mean in a normal range, should be considered a basis for further studies.

The present study was retrospective and is thus of limited value in predicting difficulty at laryngoscopy in unselected patients. Wilson and colleagues [7] and Bellhouse and Doré [8] sought to predict difficulty with tracheal intubation from simple tests suitable for routine clinical use. The "ease of intubation" angle seems to be a sensitive index of difficulty and is comparable to a similar measurement in Bellhouse and Doré's paper (the V16/V19 factor). Four of the five risk factors in Wilson and colleagues' paper (head and neck movement, jaw movement, receding mandible and buck teeth) could be seen to affect this angle directly, suggesting it may be of potential use in prospective screening. A further study showed that, as well as varying with head and neck posture, EoI showed a maximum value when the patient was placed in the proposed standard intubating position [9].

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PAIN RELIEF AFTER THORACOTOMY

I. D. CONACHER

Thoracic surgery continues to evolve, with improving techniques and technology. Carcinoma of the bronchus is the main indication for pulmonary surgery in the United Kingdom and, despite advances in chemotherapy and radiotherapy, surgery remains the only treatment with a proven record of cure. Laser resection, which minimizes the amount of lung tissue that needs to be removed, is a promising technique. It is now possible to excise small lesions, previously removable only with significant quantities of pulmonary tissue [Morritt, personal communication]. The detrimental effects of surgery on pulmonary function and reserve tend to lessen as techniques improve, so that patients presenting for surgery who have limited pulmonary reserve are becoming commonplace.

Increasingly, the critical factor in determining a patient's ability to withstand surgery is the handicap imposed by postoperative pain after obligatory thoracotomy. In order to identify vulnerable patients (those without sufficient reserve to withstand the additional burden of pain after operation), it has become necessary to redefine our criteria of "fitness for operation". Traditional rules of thumb predict the quantity of lung tissue that will remain after surgery on the basis of simple pulmonary function tests. They do not, however, predict what mass of lung tissue will be available for gas exchange. These guidelines must be modified, therefore, to allow for the immediate effects of postoperative pain on pulmonary function.

PHYSIOLOGY OF POST-THORACOTOMY PAIN

Pain is associated with shallow breathing and inability to cough. Some of the known relationships between pain and pulmonary function, such as reduction in spirometric values, functional residual capacity and closing volume, were established by studies on patients undergoing upper abdominal surgery. They indicate the development of a restrictive pattern of ventilation with reduced lung compliance. If it develops, hypoxaemia results from shunting of pulmonary arterial blood through atelectatic areas of lung leading to ventilation/perfusion inequalities. However, these effects are not caused solely by perception of pain. Other contributory factors that follow abdominal surgery include diaphragmatic splinting and abdominal distension. Additional factors after thoracic surgery include lung trauma, altered architecture, local pulmonary oedema, increased airways resistance and respiratory muscle dysfunction. So many factors are involved in reducing pulmonary reserve that the relative contribution made by pain is uncertain.

Practical methods of assessing pulmonary function at the bedside make use of simple spirometric devices. A consensus view is that the reduction in values of peak flow rates and timed forced expiratory volumes is of the order of 75% (compared with preoperative values) in the period immediately after lateral thoracotomy [3]. How much of this measurable disability is caused by, or reflects, pain?

In an early attempt to answer this question, vital capacities following implementation of an analgesic technique were expressed as a fraction of the preoperative value, and designated as a "respiration restoration factor". This concept is too simplistic because effort-derived data, such as vital capacity and peak flow rates, are non-specific. Even relatively pain free patients (those with 10-cm visual analogue scale scores of 0–3) rate a low respiration restoration factor when hindered by a

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splinted chest wall and the chest drains associated with thoracic surgery. Using simple tests, most researchers have been unable to demonstrate consistent differences in pulmonary function between patients in pain and those in whom pain has been managed effectively.

In a few studies in which preoperative effort-elicited spirometry was compared with values after surgery, differences of 15–20% were achieved when analgesia was effective. Therefore, a similar proportion of any postoperative disability may be caused by pain, and successful management of pain may recruit an equivalent mass of functioning lung tissue. To a patient undergoing pneumonectomy, such an improvement in gas exchange would be equivalent to the preservation of a whole pulmonary lobe.

It is important to appreciate that attempts to achieve effective analgesia should be directed not only towards preservation of functioning lung tissue for the vital 24–48 h after surgery. It is to be expected that effective analgesia prevents the further decline of pulmonary function which leads to a clinically significant degree of hypoxaemia and hypercarbia. Although some degree of hypoxaemia is an inevitable consequence of surgery and anaesthesia [39], the sequence of events leading to hypoxaemia (atelectasis and shunting, consequent upon shallow ventilation and failure to cough) may be preventable. An integral part of the design of any analgesic regimen should be to allow the patient to take deep expansive breaths, cough sufficiently effectively to clear airways and shift accumulating secretions and co-operate with physiotherapy in so-called "stir up" regimens. These are an antidote to some of the influences that contribute to secondary hypoxaemia and may prevent the development of alveolar hypoventilation and hypercapnia. Although some patients with compromised pulmonary function must be managed initially with controlled ventilation, it is imperative that spontaneous breathing is re-established as quickly as possible, because prophylactic measures must be implemented early if they are to be effective.

ANATOMY OF POST-THORACOTOMY PAIN

The skin incision for a postero–lateral thoracotomy usually starts posteriorly at the level of the second or third thoracic dermatome and extends anteriorly in an arc traversing a further seven dermatomes. Diathermy is used to control bleeding points. Latissimus dorsi, serratus anterior, pectoralis major and intercostal muscles are either cut or retracted. The intercostal space selected for surgical access is distracted with heavy-duty, metal retractors anchored to the ribs. The ribs may be split or fractured, the rib periosteum may be stripped, and the costo–transverse ligaments are cut or avulsed. The intercostal nerves may be damaged at this stage of operation or later when sutures or wires are passed around ribs close to the neurovascular bundle, lying in the intercostal groove. The shoulder joint may be hyperextended. All these structures are richly innervated. At the end of operation, one or more large-gauge chest drains are inserted through separate incisions in the chest wall.

Considerable pain may follow such a procedure. It is generated from several sources, both during and after operation; these include soft tissue injury and inflammation, bone and joint trauma, and visceral damage. Pain is exacerbated by movement—especially by the obligatory movements of ventilation. Occasionally, a characteristic neuritic pain from damaged intercostal nerves is discernible.

The degree of pain is rated generally as "severe". Previously, the pain of thoracotomy has been described as near the top of a league of iatrogenic causes [20]. Personal observation has rated it at 7–10 on a 10-cm visual analogue scale in patients who, before operation had volunteered grade 10 ("the worst pain imaginable") to describe their own previous experience of renal colic, acute cholecystitis, claudication or intercostal herpes zoster. Occasional patients appear to suffer little pain after operation, but far fewer than the 20% observed by Loan and Morrison in a general population of surgical patients [20].

Postero–lateral thoracotomy is the most painful of the routes for surgical access. Median sternotomy is notably less painful, but access to some intrathoracic structures may be limited. It has been claimed that vertical axillary thoracotomy provides equally good access and is less painful [1]. Use of such alternative routes is worth considering when it is judged that a particular patient may be compromised by postoperative pain.

Most of the nociceptive output generated by postoperative pain is conducted centrally to the sensorium via three well recognized routes: stimuli from the structures of the chest wall and most of the pleura pass along the intercostal nerves; those from the diaphragmatic pleura use the phrenic nerve, while those from lung and mediastinum, including the mediastinal pleura, are carried by the vagus nerve. The role of sympathetic nerves in the conduction of visceral nociception is ill defined, although they are recognized as routes for cardiac-generated pain.

ANALGESIA FOR POST-THORACOTOMY PAIN

A logical approach to the relief of pain after thoracic surgery should avoid the use of opioids, thus avoiding the dangers of respiratory depression in this vulnerable group of patients. For the majority of patients undergoing thoracotomy, the principal nociceptive routes may be blocked selectively with local anaesthetic agents, while soft tissue, bone and joint pain can be treated with simple analgesics and non-steroidal anti-inflammatory drugs (NSAID).

Regional techniques

The role of the phrenic nerves in controlling motor function of the diaphragm makes them unsuitable for block unless the technique is selective for sensory pathways. Such a refined technique for vital mixed nerves (phrenic and vagus) may not be too far-fetched. It has been suggested that inter- and intra-pleural local anaesthesia may be of value in the management of post-thoracotomy pain [33]. The mechanism of action has yet to be elucidated, but it may be partly a result of topical block of small sensory nerve endings in the diaphragmatic and mediastinal pleura.

Local anaesthetic block of the vagus nerve, at the root of the neck, has been advocated for tracheal and thoracic surgery [22]. The consequent abolition of the cough reflex was described as "striking". Clearly, no matter what improvement in analgesia might be achieved, such an effect is both undesirable and unwarranted.

Because of their proximity, the intercostal nerves and the sympathetic chain may be blocked at the same time, either by central spread from the intercostal space into the paravertebral space [38] or as a result of extradural block. Therefore, local anaesthetic block is a practical proposition.

Using a strategically sited catheter for drug placement, the duration of action of a local anaesthetic agent may be prolonged and fluctuations in analgesic effect prevented. Catheters have been placed in intercostal spaces [10, 28, 29, 31, 34], in paravertebral spaces [7, 11, 26] and in the thoracic extradural space [8, 13, 17, 25]. Spread of solution from the point of injection is variable [5], but it is often extensive. The extent of block tends to increase with volume of solution and time. Injection into one intercostal space [10, 27] or a paravertebral space [7, 11, 26] often results in a sensory block extending over several dermatomes.

For the somatic pain of thoracic surgery, the analgesic benefit from extradural block is similar to that from intercostal block, with medial spread of local anaesthetic. Generally, bilateral block is more likely to occur when the catheter is placed near the midline [8, 26].

Currently, the balance of argument is for an anatomical compromise. Catheterization of the paravertebral space is favoured in order to achieve certain, widespread and unilateral intercostal nerve block. The block is sufficiently central to block afferent pathways in the lateral division and the posterior ramus of the spinal cord which subserve damaged structures in the posterior intercostal space [6, 11]. The ipsilateral sympathetic chain is affected as it traverses the paravertebral space. Side effects such as motor block, and complications such as hypotension tend to be of a lesser degree as they, too, are primarily unilateral in both origin and effect [6, 26]. Thus compensatory reflexes and mechanisms are not altogether compromised. Also, there are benefits from paravertebral block of intercostal nerves before the onset of surgery. Pressor responses [6], and possibly the metabolic consequences of pain, are reduced. Preoperative intercostal block may result in a reduced incidence of problems associated with deafferentation [6].

Direct cryolesioning of intercostal nerves near the angle of a rib during surgery was popular for a time [12, 18, 19, 24, 30, 32] and analgesia may last for the 3 months it takes the nerves to recover. Originally considered to be a technique without complication, it has since been reported by several authors to have an association with deafferentation symptoms and scar discomfort long after operation [4, 12].

A consequence of effective intercostal nerve block is that it brings to the fore some of the other constituents that make up the post-thoracotomy pain complex. For instance, patients may become aware of the shoulder tip pain caused by diaphragmatic irritation or the deep-sited discomfort caused by mediastinal irritation and chest drain pain [8]. It is for these "revealed" pains that other techniques of analgesia are necessary.

Non-steroidal anti-inflammatory drugs

The severity of pain in the immediate postoperative period makes the use of simple analgesics inappropriate. The main benefit of drugs such as the salicylate derivatives or paracetamol is in relief from relatively minor discomforts or recuperation after chest drains have been removed.

There is good evidence that NSAID, in conjunction with other analgesic techniques, have a useful and complementary role [14, 19, 35]. They are useful for bone and joint pain when opioids may not be effective. Their peripheral action, anti-inflammatory activity and the convenience of administration by suppository are notable advantages. Administration results in improved pain relief and is associated with comparative improvements in postoperative pulmonary function [19]. There is some preliminary evidence [Rhodes and co-workers, unpublished observations] that, when given as premedication, they reduce the amount of pain experienced in the immediate postoperative period. This is presumably caused by an inhibitory action on substances such as prostaglandins, released during surgery to modulate both inflammatory and nocigenic responses.

Opioids

It has been claimed that alternative analgesic regimens are opioid sparing [8, 9, 14, 19, 32], but not substitutes. The central, sedative and anxiolytic properties of opioids promote rest and sleep. Their deliberate use, to obtund consciousness and promote respiratory depression, is of course an essential technique of thoracic anaesthesia. In occasional patients, and subject to the limitations mentioned previously, they may be used freely with artificial ventilatory support continuing into the postoperative period. Indeed, this may be the only realistic option for patients in whom the calculated pulmonary reserve is insufficient to enable them to withstand any degree of pain, or those who have undergone extensive and prolonged thoracic surgery (e.g. bilateral thoracotomy, or laparotomy plus thoracotomy).

The relative merits of different routes and methods of administration of opioids have been the subject of much debate. The i.v. route is the most practical and convenient in modern high dependency units, and the important side effects are predictable. Patient-controlled devices have proved popular as they also relieve the patient from some of the anxieties related to a sudden, almost total dependence on busy (and occasionally unsympathetic) staff. These devices currently set the standard of analgesia against which other regimens should be compared.

Neuraxial placement of opioids has been advocated [2, 12, 15, 21, 37, 40]. The most effective site remains undetermined, but it would appear that the lumbar extradural space is as suitable as the thoracic [37, 40]. In practice, catheters are placed more easily in the lumbar space. It is still difficult to judge if these techniques result in significant improvements in the quality of pain relief or a significant sparing of pulmonary dysfunction over and above that which can be achieved with continuous i.v. opioids, or both. Generally, improvements have been reported by comparison with control patients who have been given intermittent i.m. injections of opioids. The use of opioid and local anaesthetic mixtures administered by continuous extradural infusion has been reported, but experience is, as yet, limited [21]. Such refinements are worthy of further evaluation, as there is evidence that development of tolerance to local anaesthetic agents may be less likely, and their duration of action may be prolonged, when used in combination with opioids [36]. However, these techniques have no detectable influence on the indicators of the stress response to surgery [36]. The use of very fine gauge catheters for prolonged subarachnoid use has yet to be established.

Other techniques

Other methods, such as acupuncture, hypnosis, transcutaneous nerve stimulation and wound infiltration have a limited place in the management of patients who have undergone thoracic surgery [3, 4]. Several methods that have some scientific basis but are inadequate to deal comprehensively with the immediate pain of a thoracotomy may be suitable for components of pain. For example, patients with a discernible neuritic element to their pain experience may benefit from transcutaneous nerve stimulation, just as those with superficial pain may gain relief following wound infiltration with a local anaesthetic agent.

Some methods require a degree of patient–therapist interaction that is difficult to achieve, and several are so time consuming that only a small proportion of patients benefit. The psychological and behaviourial emphasis implied in the term hypnosis can be promulgated usefully by nurses and physiotherapists without resort to the formal implementation of techniques involving suggestion and relaxation.

DISCUSSION

The combined use of local anaesthesia, NSAID and opioids for the relief of post-thoracotomy pain is based on sound principles. In terms of patient comfort, excellent results have been reported when such triple-component analgesic regimens are used after abdominal surgery [35]. In practice, despite the compelling logic for using such a regimen, application to every post-thoracotomy patient may be difficult. Some of these difficulties relate to the patient population; some are a consequence of the site of surgery. Other major factors are the recovery environment and, most important of all, the analgesic drugs used.

In 1944, R. M. Waters commented that "*Relief from pain is purchased always at a price. The price both in morbidity and mortality does not greatly differ whatever the agent or agents used*". This quotation no longer adorns the fly-leaf of current editions of the late J. A. Lee's *A Synopsis of Anaesthesia*—perhaps because there are now some doubts as to its validity. Nevertheless, Waters' reference to the human cost of analgesic regimens remains apt and pertinent.

The side effects of local anaesthesia include motor block with muscle dysfunction and paralysis, and sympathetic block with hypotension and haemodynamic instability [8, 17, 26, 38]. Young and healthy patients with bilateral intercostal motor paralysis to the level of the 6th thoracic dermatome are not compromised except under extreme conditions such as those imposed by exercise [16], but it must be assumed that such motor paralysis, compounded by an associated diaphragmatic dysfunction, may significantly affect ventilatory function in those already weakened by thoracic surgery.

Several studies have suggested that thoracic extradural block may be contraindicated in patients who have undergone pneumonectomy [8, 17]. This is because of a high incidence of hypotension, and because these patients are more likely to be compromised by corrective measures such as volume loading and infusion of inotropic drugs [8].

NSAID are often contraindicated. This is because they may cause gastrointestinal haemorrhage, bleeding diatheses, hypertension and renal failure, and the thoracic surgical population includes many patients who are particularly vulnerable: for example, patients with dyspepsia presenting for upper gastrointestinal surgery, many patients with concomitant cardiovascular disease, smokers and the aged.

Opioids provide the mainstay of analgesic regimens, and their use is mandatory, but at the "price" of respiratory depression: the more effective they are, the more likely it is. The best prophylaxis in a spontaneously breathing patient is a vigilant attendant. Regular recording of ventilatory frequency, pain score and oxygen saturation are the minimum requirements for safe practice. Also, it is essential that blood-gas tensions are measured, if necessary at short intervals.

The use of neuraxial opioids has led to many reports of side effects—a few bizarre, but most previously recognized as unusual. The formulation of drugs for this route may be complicated and the economics of prescription are different. Pruritus, prolonged nausea and urinary retention require treatment. Respiratory depression remains the principal hazard, and is a particular problem because its onset may be both unheralded and prolonged [3]. Unfortunately, the vigilance of nursing staff may not be adequate to prevent episodes of severe arterial desaturation.

The patho-physiological consequences of thoracic surgery are intimately associated with postoperative pain, and potent analgesics are required if a characteristic decline in pulmonary function is to be prevented. The singular i.v. administration of opioids results in basic but, for most individuals, adequate analgesia. Although pain may be relieved, decline in postoperative pulmonary function may not be prevented. It remains to be established if the cost:benefit ratio for neuraxial opioids justifies their routine use. Regional anaesthesia is associated with problems peculiar to patients who have undergone pulmonary operations, and the use of NSAID may be restricted because of conditions that are common in the thoracic surgical population.

There is some evidence that combinations of drugs result in improved pulmonary function. The dose requirements for opioids are reduced by local anaesthetic techniques and by the use of NSAID, therefore reducing the potential for respiratory depression. It is difficult to make fair comparisons of different regimens, but it seems likely that the best results are seen in patients who receive (and can tolerate) a balanced mixture of opioids, NSAID and local anaesthetics.

It appears likely that the presurgical implementation of an analgesic regimen may lessen the severity of postoperative pain [23], and this may become a standard feature of clinical management.

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FACTOR ANALYSIS IN PATIENTS WITH A HISTORY OF FAILED TRACHEAL INTUBATION DURING PREGNANCY

L. FAHY, W. A. HORTON AND P. CHARTERS

SUMMARY

Eight patients with a history of failed tracheal intubation during pregnancy were investigated by x-ray laryngoscopy after delivery. Partial elevation of the epiglottis with no view of glottic structures was found in five patients who were therefore considered to still present difficulty. In each of these five patients the blade tip failed to make contact with the hyoid and in four this was explained by the tongue being compressed into a pear shape such that it prevented sight of the larynx. Relatively few abnormal anatomical indices were seen in these patients and this was in keeping with the level of difficulty encountered. An angular measure of jaw protrusion from a line joining the upper incisors and a point just above and anterior to the vocal cords, to the mid-point on the inner surface of the mandible was useful: the lower angle of this triangle was as important as the angle at the incisors.

KEY WORDS

Intubation tracheal. complications. Anatomy· cervical vertebrae, mandible, larynx

Patients presenting difficulty at laryngoscopy during the later stages of pregnancy are sometimes assumed not to be difficult when not pregnant. Certain factors may be peculiar to the later stages of pregnancy (such as mammamegaly, oedema of the larynx, a floppy large tongue and the wedged position), and anxiety about failed intubation, aspiration and maternal death on the part of the anaesthetist is also important [1]. X-ray laryngoscopy was used to investigate the soft tissue factors in a group of these patients.

METHODS AND RESULTS

Over a 4-yr period (1983–86), the Anaesthetic Events Records of a District General Hospital with 4500 deliveries per annum, contained 12 cases of difficult tracheal intubation in pregnancy. (This was estimated as an incidence of 1 in 140 general anaesthetics in the Maternity Unit.) Following local Ethics Committee approval, 10 of these patients were traced and, after explanation, eight agreed to take part in the study. Their mean age was 34 yr (range 28–44 yr) and the patients were investigated between 1 and 4 yr (mean 3 yr) after the time of delivery.

The original reports did not usually allow a laryngoscopy grading to be inferred with accuracy, but in each patient it was clear that a failed intubation procedure had been undertaken because of difficulty at laryngoscopy, no view of the vocal cords having been obtained. The anaesthetists concerned were of at least registrar grade with a minimum of 3 years' anaesthetic experience. The obstetric procedures were: retained placenta (three), postpartum sterilization (one), vaginal extraction (for breech) (one), Caesarean section (three, one of which was elective). In only one patient was difficulty with intubation anticipated.

The x-ray laryngoscopy technique and the laryngoscopy grading were as reported for our group of abnormal patients, and the results were analysed in the same way. The reader is referred to an accompanying paper [2] for an explanation of methodology and terminology. Approximation to the standard intubating position during x-ray laryngoscopy was confirmed in each subject by

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TABLE I. *X-ray features, neck and jaw characteristics. Abnormal indices are as defined previously* [2]*:* *$P < 0.05$. *EoI° = "Ease of Introduction" angle: Com° = "complementary" angle*

Subject No.	Grade	EoI °	Com °	X-ray features	Soft tissues	Jaw comment
1	E2	14.5	8.0*	—	—	Large JIT*
2	E2	10.5*	8.0*	Relatively large tongue (hyoid asymmetrical)	—	—
3	E2	13.5	8.5*	Unusual curved epiglottis Air gap anterior to tip	—	—
4	E3	20.5	13.5	—	—	—
5	E2	9*	6.5*	Relatively large tongue	Short neck*	Short mandible/ maxilla*
6	E4	9*	6.5*	Very short epiglottis	—	—
7	E3	18	11.5	—	—	—
8	E2	17	11.5	Relatively large tongue	Bull neck*	—

"face line" and "tracheal alignment" measurements. Cervical vertebral alignment was variable and only patient No. 6 exhibited the expected normal pattern—straight until C4 and progressively increasing extension above.

The main results are documented in table I. Close proximity of the blade tip to the hyoid body occurred in three patients in whom the view was grade E3 or E4. Patient No. 3 had an airspace between the blade tip and the hyoid and an unusually angled epiglottis. The airspace was probably caused by a "V-shaped" hyoid bone which occurs in 5% of normal subjects [3]. In the remaining four patients the blade tip was well back from the body because of the previously described "partial peardrop" effect [2].

Comparison with expected mid-line angles showed that only VOI and IST differed from normal ($P < 0.01$ and $P < 0.05$, respectively). The mandibular symphysis protruded less than in normal subjects, but mouth opening was similar. In the IST triangle comparisons, "Ease of intubation" angle (EoI) and "complementary" angle differed equally from normal values ($P < 0.01$, in each case). One or both of these angles was reduced in five patients and this corresponded with a restricted view of the larynx in all except patient No. 6 in whom the posterior commissure was visible. This patient had a particularly short epiglottis. Patient No. 8 had normal EoI and complementary angles, despite being the only patient considered clinically to be an obvious difficult intubation risk. Relative to the space available, the tongue was large in three patients (Nos 2, 5 and 8), so that the major part of its posterior surface was in contact with the posterior pharyngeal wall during laryngoscopy.

COMMENT

In 1985 Lyons described a series of eight failed intubations which occurred in the late stages of pregnancy [4]. Five had lateral x-rays of the cervical spine and abnormalities accounted for the difficulty in two. Four underwent indirect laryngoscopy by an Ear, Nose and Throat surgeon and were considered normal. The present study indicates that such assessments may not be helpful because the peardrop effect occurs only as a result of direct laryngoscopy. X-ray laryngoscopy demonstrates the contribution of soft tissue factors to the difficulties encountered on direct laryngoscopy.

Unusual angulation of the epiglottis has been demonstrated with magnetic resonance imaging and suggested as a cause of tracheal intubation difficulty [5]. This was evident in patient No. 3 (but not suspected during laryngoscopy). A V-shaped hyoid could account for the additional finding of an unexpected airspace between the blade tip and hyoid body in this patient, as this would limit approximation. There was indirect evidence to support this explanation because, anatomically, the hyoid is described as fitting into the inner surface of the mandible and, from traced lower border outlines, this was the most V-shaped of any mandible in our three reported study groups.

Comparison between these results and those for the abnormal group is instructive. Fewer indices of abnormality were found in this study but, even so, only two patients had no abnormality as judged by the indices and both were E3, which we have described as minimally difficult. In contrast, more difficult cases tend to have a number of abnormalities as defined by the objective assessment indices, and further experience refining this simple approach may be expected to improve its discriminating potential.

Several women who do not appear to be at risk of difficulty with tracheal intubation have been shown to be difficult when not pregnant; soft tissue factors were important. If the tongue appears large for the space available in the non-pregnant state, any further increase in size may have important implications for intubation during pregnancy. When soft tissue factors contribute to difficulty this may imply more room for manoeuvre than with rigid restrictions (such as limited mouth opening). Most commonly, however, there is a combination of factors and the appearance of the tongue is as large relative to the space available rather than one of absolute macroglossia.

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MYOTONIC AND NEUROMUSCULAR BLOCKING EFFECTS OF INCREASED DOSES OF SUXAMETHONIUM IN INFANTS AND CHILDREN

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SUMMARY

The myotonic effects and duration of action of several doses of suxamethonium were determined in 24 infants and 16 children during thiopentone–fentanyl–nitrous oxide anaesthesia. Infants received suxamethonium 2, 3 or 4 mg kg^{-1}; children received 1 or 2 mg kg^{-1}. The increase in muscle tone during onset of neuromuscular block was independent of dose. Onset of block was faster in children who received suxamethonium 2 mg kg^{-1} compared with those who received 1 mg kg^{-1}, and in infants given 2 mg kg^{-1} than in children given the same dose. Compared with adults given suxamethonium 1 mg kg^{-1}, infants required 3–4 mg kg^{-1} and children at least 2 mg kg^{-1} to produce 6–8 min of neuromuscular block. These results provide a clear indication for increasing the intubating doses of suxamethonium in infants and children, and a explanation for the unduly high rate of "masseter spasm" in some paediatric centres.

KEY WORDS

Anaesthesia: paediatric. Neuromuscular relaxants. suxamethonium. Complications: masseter spasm.

In an earlier study on the potency of suxamethonium in paediatric patients, we showed that infants required approximately twice as much and children 20% more than adults, on a weight basis, to produce a similar degree of neuromuscular block [1]. In view of the marked individual variability in response to suxamethonium, we suggested that the doses for intubation should be increased from 2 to 3 mg kg^{-1} for infants and 1 to 2 mg kg^{-1} for children. In the present study, we have compared the myotonic and neuromuscular blocking effects of standard and increased doses of suxamethonium in infants and children during thiopentone–fentanyl–nitrous oxide anaesthesia.

METHODS AND RESULTS

Following Ethics Committee approval, we studied 40 healthy surgical patients: 24 infants aged 9 days–10 months and 16 children aged 1–7 yr.

No premedication was given to the infants; older children received trimeprazine 3 mg kg^{-1} 2 h before operation. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and fentanyl 1–3 µg kg^{-1}, and maintained with 70% nitrous oxide in oxygen, supplemented with thiopentone as required. Intubation of the trachea was performed without the aid of neuromuscular block. Ventilation was controlled and end-tidal carbon dioxide tension was maintained at 5.0–5.5 kPa. Rectal temperature was maintained at 36.5–37.5 °C.

Neuromuscular transmission was monitored using the method described previously [1]. Briefly, the ulnar nerve was stimulated at the wrist using surface electrodes. Trains-of-four were repeated every 10 s and the resulting force of thumb adduction was recorded.

Following a period of 6–10 min to allow stabilization of the train-of-four responses, suxamethonium was administered by rapid i.v. injection. Infants were allocated randomly to three subgroups of eight, to receive suxamethonium 2, 3 or 4 mg kg^{-1}, preceded by atropine 20 µg kg^{-1}. Children were allocated randomly to two groups of eight to receive suxamethonium 1 or 2 mg kg^{-1} without prior administration of atropine.

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TABLE I. *Mean* (SEM) *[range] degree of myotonia, onset and recovery times following suxamethonium (Sux.). Significant differences:* ***$P < 0.001$ *between infants and children;* †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ *between subgroups of infants and children;* ‡$P < 0.05$, ‡‡$P < 0.01$ *between infants and children given suxamethonium 2 mg kg*$^{-1}$

	n	Maximum myotonic effect (% control)	Time from injection to 95% block (s)	Time from injection to 5% recovery (min)	Time from injection to 90% recovery (min)
Infants					
Sux. 2 mg kg^{-1}	8	21 (4)***	28 (2)‡ [21–40]	4.1 (0.3)†‡‡ [2.8–5.4]	6.5 (0.5)†‡‡ [4.2–8.3]
Sux. 3 mg kg^{-1}	8	17 (5)	32 (3) [21–38]	4.6 (0.6) [2.5–8.1]	7.4 (0.8) [5.0–12.4]
Sux. 4 mg kg^{-1}	8	24 (4)	31 (3) [19–40]	6.9 (0.5) [4.3–8.8]	10.2 (0.9) [5.9–13.3]
Children					
Sux. 1 mg kg^{-1}	8	6 (1)	46 (3)† [39–65]	3.5 (0 4)†† [2.4–6.3]	6.2 (0.5)††† [4.2–9.0]
Sux. 2 mg kg^{-1}	8	4 (1)	36 (3) [27–49]	5.8 (0.4) [4.6–7.4]	9.7 (0.7) [7.2–12.1]

Elevation of the baseline, expressed as a percentage of the control twitch, was used to measure the myotonic effect of suxamethonium. Onset of neuromuscular block was measured from injection of suxamethonium to 95% depression of the first twitch of the train-of-four sequence. Duration of action was measured from injection to 5% and 90% recovery of the first twitch of the train. Significant differences between the groups were determined using analysis of variance and Student's t test. The null hypothesis was rejected at $P < 0.05$.

No significant difference was found in the degree of increased muscle tone produced by different doses of suxamethonium (table I). However, in agreement with our earlier observations, maximum myotonic activity was significantly greater in infants than in children.

Onset of neuromuscular block was faster in children who received the larger of the two doses of suxamethonium, but there were no significant differences in onset times between subgroups of infants (table I). Both onset and recovery were faster in infants than in children given the same dose of suxamethonium (2 mg kg^{-1}). Increasing the dose of suxamethonium increased the duration of neuromuscular block in all patients, but the train-of-four ratio remained greater than 95% throughout recovery, indicating that none developed phase II suxamethonium block [2].

COMMENT

The finding that the mean increase in muscle tone following administration of suxamethonium was independent of dose is in agreement with recent work on jaw tension in adults [3]. Interestingly, the increases observed were only 60–100% greater than those we observed previously with 10% of the doses used in the present study. This suggests that there is a ceiling to the myotonic effect of suxamethonium which is exceeded by all clinically-used doses.

Although the increase in muscle tone was significantly greater in infants than in children (table I), this result may reflect differences in the attenuation of the transducer signal. Twitch tension was frequently less in infants, so that greater amplification was required. However, this should not invalidate comparisons between patients of similar ages who received different doses of suxamethonium.

In adults, a standard i.v. dose of suxamethonium 1 mg kg^{-1} is followed by a period of complete neuromuscular block lasting 6–8 min [4, 5]. Comparison with the recovery times shown in table I indicates that the equivalent doses of suxamethonium in paediatric patients are 3–4 mg kg^{-1} for infants and at least 2 mg kg^{-1} for children. These doses are somewhat greater than would be expected on the basis of potency alone [1], and indicate that rapid redistribution of the drug away from its site of action may be significant in determining the shorter duration of action in younger patients.

The finding of a very brief recovery time in children given suxamethonium 1 mg kg^{-1} supports our earlier suggestion that underdosage is the principal cause of the high incidence of "masseter spasm" seen in some childrens' hospitals [1]. Optimum conditions for tracheal intubation exist when the first twitch of the train-of-four is less than 5% of control [6]. Subtracting the time to 95% block from the 5% recovery time in table I indicates that, in children given suxamethonium 1 mg kg^{-1}, this period averaged less than 3 min, with a minimum of 1.7 min. Thus many children given the standard adult dose of suxamethonium may undergo tracheal intubation at a time when effective neuromuscular block has worn off. The adoption of 2 mg kg^{-1} of suxamethonium as the minimum intubation dose in children should reduce this problem substantially.

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PREVENTION OF HYPOTENSION FOLLOWING SPINAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION BY WRAPPING OF THE LEGS

S. BHAGWANJEE, D. A. ROCKE, C. C. ROUT, R. V. KOOVARJEE AND R. BRIJBALL

SUMMARY

Twenty-four parturients undergoing elective Caesarean section were allocated randomly to have the legs wrapped with elasticated Esmarch bandages immediately following spinal anaesthesia or to serve as controls. Significant hypotension (systolic arterial pressure < 100 mm Hg and < 80% of baseline value) was treated with i.v. ephedrine in 5-mg boluses. Leg wrapped patients had a significantly (P = 0.0033) lower incidence (16.7%) of hypotension than controls (83.3%). Only two patients in the leg wrapped group required ephedrine compared with 10 in the control group. Systolic arterial pressure was significantly (P < 0.05) less in control subjects at 4, 5 and 6 min following spinal injection. No patient in the leg wrapped group became hypotensive following removal of the elasticated bandages.

KEY WORDS

Anaesthesia, obstetric. Anaesthetic techniques, spinal. Complications: hypotension.

The incidence and severity of spinal hypotension may be reduced by administration of a crystalloid preload and the use of left lateral tilt [1]. Whilst these measures should be considered mandatory, they do not prevent completely the occurrence of hypotension, and administration of a vasopressor is often required. We have investigated leg compression using elasticated Esmarch bandages as a method of reducing the incidence and severity of post-spinal hypotension at Caesarean section.

METHODS AND RESULTS

Twenty-four healthy term mothers undergoing elective Caesarean section under spinal anaesthesia gave informed consent to participate in the study, which was approved by the local Ethics Committee. Patients with placental dysfunction, intrauterine growth retardation, abnormal fetal presentation or who weighed more than 90 kg were excluded. Patients were allocated randomly to two groups; group I ($n = 12$) had their legs wrapped immediately following subarachnoid injection of the local anaesthetic solution. Group II patients ($n = 12$) did not have their legs wrapped and acted as a control group.

Upon entering the operating theatre, fluid preloading was commenced (Plasmalyte L, 20 ml kg^{-1}, pregnant weight) and baseline heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure measured and recorded with patients in left lateral tilt position. The same dedicated non-invasive arterial pressure monitor (Critikon Dinamap) was used in all patients. The mean of three readings at 3-min intervals was taken as the baseline value provided that SAP did not vary by more than 10%.

Following completion of baseline readings, patients were positioned on the operating table in the sitting position and plain 0.5% bupivacaine 1.5 ml was injected over 10 s through a 25-gauge needle into the subarachnoid space at the L3–4 interspace. Immediately thereafter patients were

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returned to the left lateral tilt position and HR, SAP and DAP recorded at 1-min intervals for 10 min and every 5 min thereafter until completion of surgery.

Immediately after repositioning, group I patients had their legs wrapped. Each leg was raised 45° from the horizontal and a 10-cm Esmarch elasticated bandage applied from the ankle to the mid thigh, where the end was tucked in to prevent unravelling. More than one bandage per leg was necessary sometimes. Each leg was wrapped in turn and the presence of adequate capillary pulsation in the toes used to ensure that arterial pressure had not been exceeded. Leg wrapping was completed within 3 min.

Hypotension was defined as a decrease in SAP $> 20\%$ from baseline in association with an absolute value < 100 mm Hg. If hypotension occurred, ephedrine was administered i.v. in 5-mg boluses at 1-min intervals until SAP returned to within 20 % of control values or more than 100 mm Hg. Neonatal condition was assessed by Apgar minus colour (A – C) score at 2 and 5 min and by umbilical arterial (Ua) and venous (Uv) blood-gas measurements. At termination of the surgical procedure the legs were unwrapped and haemodynamic variables recorded at 1-min intervals for 10 min.

Data were analysed using paired and unpaired *t* tests and Fisher's exact probability test as appropriate.

Groups were comparable for maternal age, weight, preload volume, mean thoracic sensory levels, spinal injection to delivery time, uterine incision to delivery time and baseline arterial pressures and heart rate.

There was a high incidence of hypotension requiring vasopressor therapy in the control group (83 %) (95 % confidence limits 50.9–98.4) compared with the leg wrapped group (16 %) (95 % confidence limits 1.6–49.1)—a difference which was significant both clinically and statistically ($P = 0.0033$, Fisher exact). Only two patients in group I (leg wrapped) required ephedrine (15 and 25 mg), whilst 10 patients needed ephedrine in the control group (three needed 5 mg, two 10 mg, three 15 mg, one 25 mg and one 45 mg, corresponding to the duration of hypotension).

In the control patients there was a decrease in SAP following spinal injection (fig. 1) which was significantly lower ($P < 0.05$) than baseline values at 3, 4, 5 and 6 min. SAP returned to baseline by 10 min and was greater thereafter, being significantly greater than baseline at 25 min. Leg wrapped patients had a small decrease in SAP between 1 and 5 min, which was not significant. The difference in SAP between the groups was significant ($P < 0.05$) at 4, 5 and 6 min.

Heart rate initially increased in both groups and was greater ($P < 0.05$) than baseline values in the control group at 1, 3, 4 and 6 min, whereas leg wrapped subjects had no significant increase (fig.

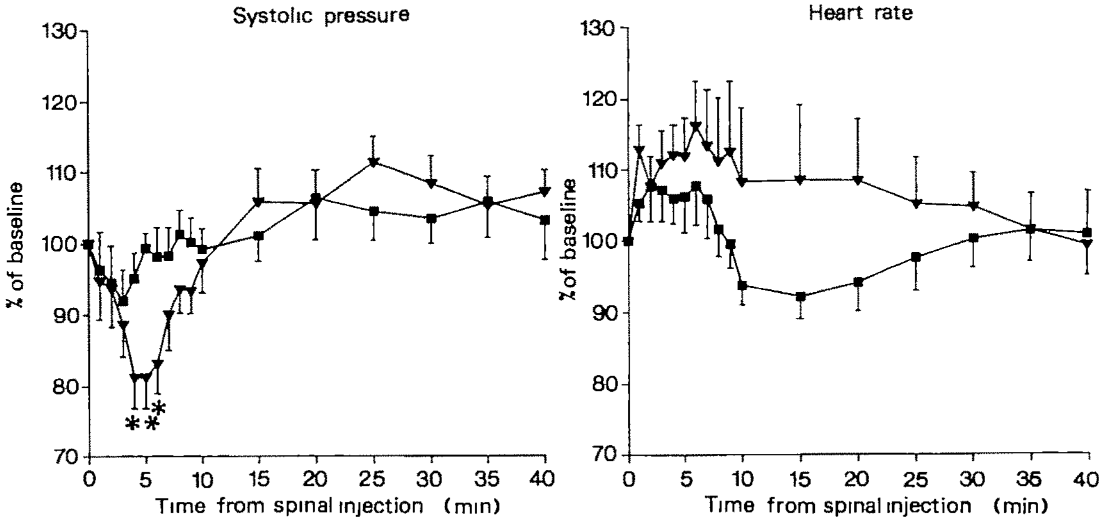

FIG. 1. Systolic arterial pressure and heart rate (mean, SEM) following spinal anaesthesia, expressed as a percentage of baseline values. *Significant differences ($P < 0.05$) between groups. See text for changes from baseline within groups. ■ = Legs wrapped; ▼ = control group.

1). HR in the leg wrapped group tended to decrease after 9 min and values at 10 and 15 min were lower ($P < 0.05$) than baseline. In the control group, HR remained increased from 10 to 30 min. The difference in HR between the groups was not statistically significant. No patient experienced hypotension following unwrapping of the legs. Papaveretum 10–15 mg i.v. was given to 22 of the patients following delivery, to provide postoperative analgesia.

All neonates were in good clinical condition at delivery. One neonate in the control group whose mother was hypotensive for 8 min had an A–C score of 7 at 2 min. There were no statistically significant differences in Ua and Uv blood-gas data between the groups; however, Ua oxygen tensions and saturations were significantly ($P < 0.05$) less in babies of mothers who developed clinically significant hypotension (hypotensive patients: Ua_{O_2} 1.9 (SD 0.49) kPa, saturation 13.9 (5.9)%; normotensive patients: Ua_{O_2} 2.5 (0.32) kPa, saturation 24.1 (6.94)%).

COMMENTARY

Hypotension following spinal anaesthesia results from a decrease in arteriolar and venous tone secondary to sympathetic block, with a consequent reduction in systemic vascular resistance and venous return [2]. As a significant contribution to the hypotension is made by venous pooling in the legs and abdomen, we investigated simple leg wrapping as a method of reducing the incidence and severity of hypotension.

Our study demonstrates that leg wrapping immediately following spinal injection resulted in a reduced incidence of hypotension and a subsequent reduction in the number of patients requiring vasopressor therapy. Two other studies have attempted to use compression of the legs to manage spinal hypotension. In 1973 James and Greiss reported their experience with inflatable boots but did not find them beneficial [3]. Their incidence of hypotension was 60% in patients managed with inflatable boots, which was the same as their control group. However, they used a much smaller preload (10 ml kg^{-1}) and did not institute left lateral tilt until after the onset of hypotension. However, they did comment that leg elevation during boot inflation may have explained the slightly later onset of hypotension in the patients wearing boots. In 1988 Goudie, Winter and Ferguson reported the use of inflatable splints in patients undergoing elective Caesarean section under spinal anaesthesia [4]. Whilst their preload was more in keeping with current practice (15 ml kg^{-1}) the incidence of hypotension remained unacceptably high (48%) in the study group compared with control (83%).

In addition to leg wrapping, simply raising the legs during the period of onset of spinal anaesthesia may have contributed to the decreased incidence of hypotension. We can find no studies on the effect of leg raising in the obstetric population, but studies of relative or absolute hypovolaemia suggest leg raising to be of little value with regard to improvement in arterial pressure or cardiac index [5]. Leg raising alone is unlikely to have played a major role as it results in autotransfusion of only 150 ml [6]. It is likely that the reduction in the incidence of hypotension by leg wrapping is caused by prevention of increased vascular capacitance by venodilatation in the legs following the development of autonomic block rather than autotransfusion of blood.

In conclusion, we have confirmed the high incidence of hypotension following spinal anaesthesia for Caesarean section despite routine preventative measures. However, unlike other authors, we have shown that the incidence of hypotension can be reduced by the use of simple leg wrapping with elasticated Esmarch bandages with a subsequent reduction in the use of potent vasopressor agents. Before widely recommending the technique, further study is required to evaluate its effect upon the severity and duration of hypotension.

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EFFECT OF PROPOFOL ON BRAIN RETRACTION PRESSURE AND CEREBRAL PERFUSION PRESSURE

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SUMMARY

We have studied the effect of propofol, at a rate of 30 mg kg^{-1} h^{-1} for 5 min reducing to 6 mg kg^{-1} h^{-1} for a further 5 min, on brain retraction pressure (BRP) in 15 patients undergoing craniotomy. The response of BRP showed two distinct patterns. BRP was reduced by an average of 3.3 mm Hg ($P = 0.005$). Mean arterial pressure was reduced in all patients by an average maximum of 28.3 mm Hg ($P = < 0.001$), which caused a significant reduction in cerebral perfusion pressure (CPP) by 22.9 mm Hg ($P < 0.001$). It is concluded that, by reducing BRP, propofol provided suitable conditions for intracranial surgery, but care should be taken to avoid excessive reduction in CPP.

KEY WORDS

Anaesthetics, intravenous: propofol. Brain. blood flow

In patients undergoing intracranial surgery, increased intracranial pressure (ICP) is important when the cranium is intact because it may cause brain shift or cerebral ischaemia as a result of reduction in cerebral perfusion pressure (CPP). When the dura has been opened, ICP decreases to zero, but the factors causing an increase in ICP by increasing brain bulk are still operative, causing a congested brain and requiring increased pressure to be applied with brain retractors in order to gain adequate surgical access. The purpose of this investigation was to measure the effects of propofol, which reduces cerebral blood flow (CBF) and ICP [1, 2], on the pressure exerted on the brain by a retractor, and to calculate the perfusion pressure of the brain under the retractor.

METHODS AND RESULTS

We studied 15 patients (ASA grade I or II) undergoing craniotomy requiring retraction of brain tissue. The study was approved by the Hospital Research Ethics Committee and informed consent was obtained from all patients.

Temazepam 20 mg was given orally for premedication; anaesthesia was induced with thiopentone and fentanyl and relaxation for tracheal intubation was produced with atracurium. Anaesthesia was maintained with 66% nitrous oxide in oxygen and incremental doses of tubocurarine and fentanyl (up to a total dose of 6 μg kg^{-1}). Enflurane in concentrations of up to 0.6% was added as necessary to maintain the systolic arterial pressure at 110–150 mm Hg. The lungs were ventilated mechanically to produce an end-tidal carbon dioxide tension of 3.5–4.0 kPa. Mean arterial pressure (MAP) was measured directly from a radial artery cannula with the transducer at heart level. Craniotomy was performed and after the dura was opened a specially modified Greenberg brain retractor was applied to the brain to give a brain retraction pressure (BRP), measured on the Albin Brain Retraction Pressure Monitor (Codman), of 20–25 mm Hg.

After application of the brain retractor, BRP and MAP were recorded for 5 min to obtain control values. An infusion of propofol was commenced at a rate of 30 mg kg^{-1} h^{-1} reducing to 6 mg kg^{-1} h^{-1} after 5 min, or earlier if MAP was less than 60 mm Hg. The infusion was discontinued after 10 min and BRP and MAP were recorded for at least a further 10 min. Arterial blood-gas samples were taken before and during the infusion of propofol.

The changes in BRP exhibited two different patterns. In nine patients (Nos 1–9, group A) BRP remained constant during the control period, decreased when propofol was administered and returned gradually to the control value after

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propofol was stopped. In six patients (Nos 10–15, group B) BRP decreased steadily during the control period, but the rate of decline increased sharply when propofol was given and, when the propofol was stopped, there was no increase in BRP. For group A, the maximum change from control value for BRP was calculated by subtracting the minimum BRP during the period of infusion of propofol from the BRP recorded before the propofol infusion was started. For group B, the control values for BRP at each time epoch were calculated by assuming that the initial rate of change in BRP was linear and that this rate would be maintained throughout the duration of the study. The maximum change from control for BRP was calculated by comparing the measured values recorded at each time epoch with the predicted values. Cerebral perfusion pressure under the retractor blade was calculated by subtracting the BRP from the MAP.

The maximum changes in BRP, MAP and CPP were compared with control values using a Student's paired t test.

BRP was reduced by an average of 3.3 mm Hg overall ($P = 0.005$), 4.7 mm Hg in group A ($P = 0.016$) and 1.3 mm Hg in group B ($P = 0.006$). MAP was reduced in all patients, with an average maximum reduction of 28.3 mm Hg ($P < 0.001$), which caused a significant reduction in CPP by an average of 22.9 mm Hg ($P < 0.001$) (table I).

In individual patients Pa_{CO_2} did not vary significantly during the period of the study. For all the patients it averaged 4.3 kPa (range 3.5–5.5 kPa).

COMMENT

This investigation has shown that propofol reduced the pressure under the brain retractor during surgery on the brain. However, this beneficial effect was at the expense of reduction in MAP and CPP. (The calculated CPP was only an estimate of the perfusion pressure under the brain retractor, as systemic rather than local arterial pressure was used for the calculation.) The initial rate of infusion used in this study was more than twice the rate of 12 mg kg^{-1} h^{-1} recommended for maintenance of anaesthesia, so the effect on MAP could be reduced by decreasing the dose of propofol. The initial rate of infusion (30 mg kg^{-1} h^{-1}) used here was chosen because, over a 5-min period, it would give the dose required for induction of anaesthesia. This produced a much greater depth of anaesthesia than necessary for maintenance of unconsciousness when using a neuromuscular blocking technique with nitrous oxide and enflurane and, in combination with

TABLE I. *Brain retraction pressure (BRP), mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) before and during the infusion of propofol. For patients 10–15 the maximum change in BRP was calculated by the method described in the text. 1 = Before propofol; 2 = minimum during infusion of propofol; 3 = maximum change after propofol*

Patient No.	BRP (mm Hg)			MAP (mm Hg)			CPP (mm Hg)		
	1	2	3	1	2	3	1	2	3
1	25	14	−11	133	100	−33	107	81	−26
2	18	14	−4	93	74	−19	71	57	−14
3	28	14	−14	84	59	−25	55	42	−13
4	9	6	−3	85	64	−21	68	57	−11
5	22	19	−3	86	40	−46	62	20	−42
6	22	21	−1	103	73	−30	80	52	−28
7	24	22	−2	96	66	−30	72	43	−29
8	9	7	−2	94	72	−22	83	65	−18
9	24	22	−2	94	60	−34	70	40	−30
10	20	—	−0.5	106	86	−20	80	67	−13
11	11.5	—	−1.5	101	65	−36	87	57	−30
12	23	—	−1	94	53	−41	70	31	−39
13	9.5	—	−0.5	69	52	−17	57	44	−13
14	14	—	−2	104	72	−32	85	62	−23
15	13	—	−2	85	66	−19	70	56	−14
Mean	18.1		−3.3	95.1	66.8	−28.3	74.5	51.6	−23
SEM	1.7		1.0	3.7	3.7	2.3	3.4	4.0	2.6
P			0.005			< 0.001			< 0.001

these agents, would be expected to produce a marked reduction in MAP.

The effects of thiopentone on the cerebral vasculature would have terminated within 10 min, and fentanyl and 0.6% enflurane do not affect the cerebral vessels, so these agents would not influence BRP. Nitrous oxide 66% in oxygen causes cerebral vasodilatation [3] so it may have reduced the effect of propofol on BRP. However, the results are clinically relevant because nitrous oxide is commonly administered during maintenance of anaesthesia with propofol infusions.

A weakness in this investigation, which also detracts from the usefulness of BRP measurements for assessing the effects of anaesthetic agents on brain bulk, lies in the tendency for a compliant brain to "creep" away from the retractor which makes interpretation of the results more difficult. Such brain movement made interpretation of the significance of the change in BRP more difficult in six patients in this study. However, even if the assumptions made in calculating the maximum change in BRP from control in these patients were incorrect, exclusion of these patients and analysis of the results only in those patients whose brains did not show creep (group A) still showed a significant reduction in BRP caused by administration of propofol. This latter group of patients included those with greater space occupation and reduced intracranial compliance, in whom a reduction in brain bulk and BRP is more important.

The mechanism of reduction of BRP by propofol is most likely cerebral vasoconstriction causing a reduction of CBF, cerebral blood volume and thus brain bulk; it is well documented that propofol reduces CBF [1, 4] and ICP [2, 5, 6]. If autoregulation of the cerebral circulation was impaired in some or all of the patients, it is possible that the reduction in MAP may have contributed to the reduction in BRP. However, the timing of the reduction in MAP did not correspond exactly with the reduction in BRP, and BRP returned to control values before MAP when the propofol was stopped.

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UNCONSCIOUSNESS ASSOCIATED WITH MIDAZOLAM AND ERYTHROMYCIN

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SUMMARY

An 8-yr-old boy suffering from an asymptomatic ventricular septal defect was given erythromycin for antibiotic prophylaxis before adenoidectomy. Sixty minutes after premedication with oral midazolam 0.5 mg kg^{-1} and oral atropine 0.03 mg kg^{-1}, an infusion of erythromycin 400 mg was started. When 200 mg of erythromycin had been infused, the patient lost consciousness, but other vital functions remained normal. After 45 min, he awakened spontaneously. At that time the plasma concentration of midazolam was 134 ng ml^{-1}. In order to investigate possible interactions between midazolam and erythromycin, we studied the pharmacokinetics of midazolam in six children of the same age undergoing minor otolaryngological surgery. The plasma concentration of midazolam in the patient who lost consciousness was significantly greater than in six other children without concomitant administration of erythromycin. The altered pharmacokinetics of midazolam may result from reduced hepatic clearance of midazolam caused by an enzyme inhibiting drug, erythromycin.

KEY WORDS

Complications. coma. Interactions erythromycin, midazolam.

Midazolam is an effective oral premedicant in children. No marked side effects have been observed after doses of 0.4–0.5 mg kg^{-1} [1]. Erythromycin inhibits metabolism of midazolam *in vitro* and has been thought to reduce its metabolism in man [2, 3]. We describe a child in whom the administration of erythromycin with midazolam (without any other medication) was associated with unexpectedly great plasma concentrations of midazolam and deep unconsciousness. The pharmacokinetics of midazolam in this patient were compared with the pharmacokinetics of midazolam in children not given erythromycin.

CASE REPORT

We aimed to give an 8-yr-old boy (ASA II; weight 27 kg) erythromycin 400 mg (Abboticin, Abbott S.A., France) in saline 100 ml i.v. before adenoidectomy because of an asymptomatic ventricular septal defect. He was premedicated with oral midazolam 0.5 mg kg^{-1} (Dormicum injection, Roche, Switzerland) and oral atropine 0.03 mg kg^{-1} in 0.7 ml kg^{-1} of fruit juice 60 min previously. On arrival in the operating theatre the child was fully awake. Heart rate was 96 beat min^{-1}, arterial pressure was not measured. Ten minutes after beginning the infusion of erythromycin, the child developed nausea and tachycardia. When 200 mg had been infused (40 min after commencing the infusion) the patient lost consciousness. He did not respond to verbal commands but reacted by withdrawal to noxious stimuli. He was breathing spontaneously and the airway was not compromised. No oral airway was inserted. The pupils were small and symmetrical.

The patient was transferred to the recovery room and the proposed operation was postponed. In the recovery room, heart rate and ECG were displayed continuously on an oscilloscope. Systolic and diastolic arterial pressure were measured using a sphygmomanometer every 5 min. Haemoglobin oxygen saturation was monitored by

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pulse oximetry (Ohmeda Biox 3700 Pulse Oximeter, Colorado, U.S.A.). The child was positioned on his side. When he was unconscious, haemoglobin oxygen saturation was 99%, systolic arterial pressure 100–120 mm Hg and heart rate 105–115 beat min^{-1}. Rectal temperature was 37.2 °C. After 45 min the child awakened spontaneously and was a little drowsy but otherwise normal. No specific or non-specific antidotes to midazolam were given. At this time, 170 min after administration of premedication, plasma concentration of midazolam was 134 ng ml^{-1}. Thereafter the concentration declined rapidly and was below the limit of detection after approximately 24 h. The area under the plasma midazolam concentration–time curve from 0 to 24 h (AUC) was 601 ng ml^{-1} h^{-1} (fig. 1). Haemoglobin concentration, erythrocyte sedimentation rate, serum C-reactive protein, aspartate- and alanine aminotransferases, gammaglutamyltransferase and calcium concentrations were within the normal range. Serum protein electrophoresis was normal, except for the gamma fraction, which was 6.2 g $litre^{-1}$ (normal range 7.0–16.0 g $litre^{-1}$).

PHARMACOKINETIC STUDY

After institutional approval and informed consent from the children and their parents we studied the pharmacokinetics of midazolam in three boys and three girls (mean age 7.7 (SD 1.1) yr, weight 28.0 (2.4) kg), all ASA grade I, undergoing minor otolaryngological surgery with thiopentone–suxamethonium or vecuronium–alfentanil–halothane and nitrous oxide anaesthesia. None was taking any other drugs. The mean duration of anaesthesia was 63 (22) min. Oral midazolam (Dormicum injection, Roche, Switzerland) 0.5 mg kg^{-1} and atropine 0.03 mg kg^{-1} in 0.7 ml kg^{-1} of fruit juice were given for premedication. Plasma concentrations of midazolam were measured before the administration of midazolam and after 30, 60, 120, 180, 240, 360 and 1440 min by gas chromatography with electron capture detection using methoxydiazepam as the internal standard [4].

The mean AUC was 214 (95% confidence interval 45–384) ng ml^{-1} h^{-1} and peak plasma concentration (*C*max) 73 (31–114) ng ml^{-1} (fig. 1).

DISCUSSION

The plasma concentrations of midazolam in children not given erythromycin were comparable to those observed in an earlier study of oral administration of the same preparation of midazolam to children [5]. Following i.m. administration of the same dose of midazolam, it may be expected that the plasma concentrations of midazolam would be greater, as the bioavailability after i.m. administration in children is higher than after oral administration [5] because of first-pass metabolism. It has been shown in children that the bioavailability of 0.45 or 1.0 mg kg^{-1} of oral midazolam is approximately 15%, whereas almost 30% of midazolam 0.15 mg kg^{-1} is absorbed after oral administration [5].

In the present study, plasma concentrations of midazolam were significantly greater in the patient given erythromycin with midazolam than in the others. Theoretically, the observed difference could be caused by methodological problems in

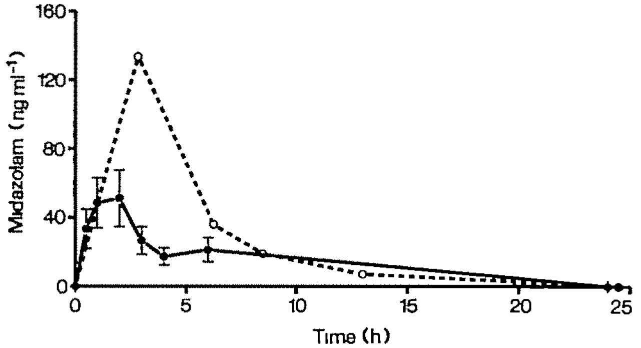

FIG. 1. Plasma concentration of midazolam in the patient given midazolam 0.5 mg kg^{-1} with erythromycin (○) and mean (SEM) plasma concentration of midazolam in six control patients given midazolam 0.5 mg kg^{-1} without erythromycin (●).

determining pharmacokinetics, an inappropriate dose, increased absorption or reduced hepatic clearance. The first child had nausea, which could result in delayed absorption of midazolam; this would explain the greater concentrations of midazolam in the postabsorption phase. The greatest concentration of midazolam in our patient, however, was significantly more than the mean *C*max in the others. Therefore, in addition to possible delayed absorption, there may have been other kinetic differences between the child receiving erythromycin and the other children. Because the dose given to the child was checked and found to be correct, accidental overdose would seem to be an unlikely explanation of our findings. Correspondingly, on the basis of the studies in adults, increased absorption of midazolam does not appear to explain the present findings [6].

Reduced hepatic clearance appears to be the best explanation of the high concentrations of midazolam in our patient. This may be a result of interindividual variation but, in our case, more probably of an interaction with an enzyme inhibiting drug, erythromycin [7]. Interaction between midazolam and erythromycin has been suspected previously in patients treated in the intensive care unit [2, 3]. In these patients, high concentrations of midazolam could not be attributed to co-administration of erythromycin because of the critical condition of the patients and because of the concomitant use of drugs other than erythromycin and midazolam.

On the basis of the present study, we suggest that care should be exercised when prescribing midazolam for patients receiving erythromycin. However, controlled studies are needed to study possible interactions between midazolam and erythromycin.

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CONCENTRATIONS OF ATRACURIUM AND LAUDANOSINE IN CEREBROSPINAL FLUID AND PLASMA IN THREE INTENSIVE CARE PATIENTS

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SUMMARY

We have measured concentrations of atracurium and laudanosine in cerebrospinal fluid (CSF) and plasma in three intensive care patients receiving atracurium infusions of 22.5–106 h duration to maintain neuromuscular block. Two patients had suffered severe closed head injuries and the third patient had developed respiratory failure following the clipping of two intracranial aneurysms. The total dose of atracurium given was 14.3–136.6 mg kg^{-1}; rate of infusion was 0.6–1.38 mg kg^{-1} h^{-1}. Plasma concentrations of atracurium and laudanosine were 0.73–3.11 μg ml^{-1} and 0.48–8.65 μg ml^{-1}, respectively; CSF concentration of laudanosine was 70–440 ng ml^{-1}. No adverse effects attributable to these concentrations of laudanosine were observed.

KEY WORDS
Cerebrospinal fluid: atracurium, laudanosine. Neuromuscular relaxants: atracurium, laudanosine.

Concern has been expressed regarding possible accumulation of laudanosine during prolonged infusions of atracurium [1]. Laudanosine has been shown to have cerebral excitatory properties in cats [2], mice and rats [3] and dogs [3–5]. In dogs, the effects vary from EEG arousal patterns at plasma concentrations of 2–4 μg ml^{-1} to clonic seizures at approximately 17 μg ml^{-1}. The greatest plasma concentration of laudanosine reported to date in man was 5.1 μg ml^{-1} [6] but no side effects were observed.

The concentration of laudanosine in the central nervous system determines cerebral toxicity, and accumulation in the CNS appears to differ depending on the species studied. In dogs, CSF concentrations increase rapidly following an i.v. bolus dose of laudanosine 1 mg kg^{-1}, and reach 30–60% of plasma concentration within 10 min [4]. In comparison, when atracurium was used to provide neuromuscular block during intracranial aneurysm surgery, after 2 h the mean CSF:plasma laudanosine ratio was 17% [7]. To date, no data have been published on the penetration of laudanosine into the CNS when atracurium infusions of more than 2 h duration are used.

We have therefore studied CSF and plasma concentrations of atracurium and laudanosine in three patients who received infusions of atracurium for periods of 22.5, 44 and 106 h, respectively.

PATIENTS AND METHODS

The study was approved by the District Ethics Committee. Three patients were receiving atracurium as part of the normal technique to facilitate controlled ventilation following cerebral injury. Sedation was provided using continuous infusions of propofol or midazolam, and fentanyl. Ventilatory minute volume was adjusted to maintain Pa_{CO_2} at 3.5–4.0 kPa, and the ECG, arterial and central venous pressures were monitored continuously in all three patients. Core temperature was 36–38 °C. There were no other associated injuries, and renal and hepatic function were within normal limits.

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Plasma concentrations of atracurium and laudanosine were measured in samples of blood obtained from an indwelling arterial catheter. Samples of CSF were obtained via a lumbar subarachnoid drain (patient A) and from ventricular catheters in the two other patients. The first 2 ml of blood and 1 ml of CSF were discarded to ensure fresh samples were obtained for analysis. Each pair of samples was centrifuged immediately at 13000 *g* for 1 min and 0.2 ml of the supernatant decanted into 0.8 ml of cooled sulphuric acid (pH 1.5) and frozen at −20 °C. Concentrations of atracurium and laudanosine in plasma and CSF were assayed in duplicate using high pressure liquid chromatography [8]. The assay was sensitive to 20 ng ml^{-1} for atracurium and 10 ng ml^{-1} for laudanosine. The coefficients of variation for atracurium were 6.6% at 1000 ng ml^{-1}, 2.7% at 2000 ng ml^{-1} and 4.0% at 4000 ng ml^{-1} and for laudanosine 7.6% at 100 ng ml^{-1}, 2.8% at 200 ng ml^{-1}, 2.3% at 1000 ng ml^{-1}, 3.2% at 1500 ng ml^{-1} and 1.9% at 8000 ng ml^{-1}.

CASE REPORTS

Patient A

A 56-yr-old, 65-kg female developed respiratory failure 24 h after uneventful clipping of a right anterior and left posterior communicating artery aneurysms. The decision was taken to ventilate her lungs artificially; this was facilitated by a bolus of atracurium 0.8 mg kg^{-1}, followed by a constant infusion at 0.6 mg kg^{-1}, with continuous infusions of fentanyl and midazolam for sedation. The lumbar subarachnoid drain inserted at the time of surgery was still functioning. Paired samples of arterial blood and CSF were obtained after 12 and 22.5 h. The lumbar drain was removed at this time, but ventilation and the atracurium infusion were continued for a total of 7 days. The CSF samples were colourless and on subsequent analysis atracurium could not be detected. The total dose of atracurium given by 22.5 h was 0.93 g (table I). After resolution of a chest infection the patient made a slow neurological recovery. Focal epileptiform seizures occurred 9 and 10 days after stopping the atracurium infusion. These were treated successfully with clonazepam. CT scan showed the presence of a small cerebral infarct.

Patient B

A 25-yr-old, 80-kg male sustained a closed head injury in a road traffic accident. On admission, his Glasgow Coma Score was 6 and there were no other associated injuries. CT scan demonstrated multiple cerebral contusions. The decision was made to ventilate his lungs and an intraventricular catheter was inserted to monitor intracranial pressure. The patient was sedated with continuous infusions of fentanyl and midazolam. For the first 8 h, repeated boluses of atracurium were given to a total of 330 mg. An infusion of atracurium was started and adjusted to ensure abolition of the cough reflex during tracheal suction. For the first 6 h the infusion rate was 0.75 mg kg^{-1} h^{-1}. It was then necessary to increase the rate to 1.0 mg kg^{-1} h^{-1}, which was maintained for the next 30 h. Paired samples of arterial blood and CSF were obtained for assay 8, 14, 20, 32, 38 and 44 h after starting ventilation. The CSF samples were colourless, and on subsequent analysis no atracurium was detected. The total dose of atracurium given during the 44-h period was 3.09 g

TABLE I. *Plasma and CSF atracurium and laudanosine concentrations for each patient*

		Plasma		CSF		
Patient	Time (h)	Atracurium (μg ml^{-1})	Laudanosine (μg ml^{-1})	Atracurium (μg ml^{-1})	Laudanosine (ng ml^{-1})	CSF:plasma ratio
A	12	0.75	0.48	—	100	0.21
	22.5	0.95	0.52	—	120	0.23
B	8	1.48	0.99	—	—	—
	14	0 85	1.09	—	70	0.06
	20	1.84	1.44	—	110	0.07
	32	2.15	2 00	—	140	0.07
	38	3.11	2 20	—	190	0.09
	44	1.36	1 83	—	170	0.09
C	106	2.78	8.65	—	440	0.05

(table I). The patient made a slow neurological recovery and there was no clinical evidence of epileptiform activity.

Patient C

A 28-yr-old, 58-kg female sustained a closed head injury during a road traffic accident. On admission, her Glasgow Coma Score was 7; there were no other injuries. CT scan showed diffuse cerebral oedema, and the decision was made to ventilate her lungs artificially. An intraventricular catheter was inserted to monitor intracranial pressure. Continuous infusions of propofol and fentanyl were used for sedation. Control of ventilation was achieved with a bolus dose of atracurium 0.7 mg kg^{-1}, followed by an infusion, initially at the rate of 0.86 mg kg^{-1} h^{-1}, which was sufficient to abolish coughing during tracheal suction. After 14 and 32 h it was necessary to increase the rate of infusion of atracurium, first to 1.21 mg kg^{-1} h^{-1} and then to 1.38 mg kg^{-1} h^{-1}. This final rate remained constant until the infusion was stopped at 106 h. Paired samples of arterial blood and CSF were taken immediately before stopping the infusion of atracurium. The CSF sample was colourless and no atracurium was detected. The total dose of atracurium given was 7.92 g (table I). The patient made a good recovery and did not experience any fits.

DISCUSSION

The plasma concentration of laudanosine causing toxic side effects has been measured in several animal species, but the corresponding values for man are not known. It has been assumed that they may be similar, although the data available suggest a species difference in penetration of laudanosine into the CNS. Previous studies in man have shown that CSF concentrations of laudanosine increase slowly, reaching 10–13 ng ml^{-1}, 60 min after a single bolus of atracurium [9], and a mean of 203 ng ml^{-1} after an infusion of approximately 2 h duration [7]. In contrast, in dogs, CSF concentrations of laudanosine reached 210–640 ng ml^{-1} within 10 min of a bolus of laudanosine 1 mg kg^{-1} [4]. The reason for these differences is unlikely to be the large dose of laudanosine administered to dogs, as the resultant plasma concentrations of laudanosine were of the same magnitude as those seen in man when an infusion of atracurium was used. These observations may represent species variation in transfer into or clearance from CSF, which in turn may account for the lack of reports of laudanosine toxicity in man, despite plasma concentrations in the range causing CNS excitatory effects in dogs.

In the present report, infusions of atracurium were used to facilitate ventilation in patients with cerebral injuries. The rate of infusion of atracurium and subsequent plasma concentrations of atracurium were similar to those described by Yate and colleagues for patients in a general ITU [6]. Patients B and C required increasing rates of infusion of atracurium to maintain a satisfactory degree of neuromuscular block, and this was described also by the above authors. The mechanism of this increased requirement is not known, but studies in dogs suggest that it may be related to the period of prolonged immobility [10].

The greatest CSF:plasma ratio occurred in patient A (0.23 after 22.5 h), who had undergone intracranial surgery, and is similar to those reported after 2 h in a series of patients at the time of surgery [7]. Although the CSF samples were obtained via a lumbar subarachnoid drain, this is unlikely to account for the difference between this patient and the two others, as it takes only 60–90 min for CSF in this region to mirror contamination of the ventricles with a foreign substance [11]. The presence of the drain is also likely to shorten this period by facilitating circulation of CSF. Although blood from the operative site may have increased the CSF concentrations of laudanosine, the samples were not blood stained or xanthochromic and atracurium was not detected.

The CSF:plasma ratios in patients B and C, who had sustained head injuries, were lower than in patient A, despite greater plasma concentrations of laudanosine. We postulate that the accumulation of laudanosine within the CNS in man may be dependent in part upon the underlying pathology. Following both subarachnoid haemorrhage [12] and head injury [13], the blood–brain barrier becomes more permeable. In addition, changes occur also in the rate of production of CSF [14]. Each of these factors may influence the final concentration of a foreign substance within the CNS. In patients with non-CNS pathology in which the integrity of the blood–brain barrier is preserved, the concentrations of laudanosine within the CNS may be even less for a given plasma concentration. This may explain the lack of reported side effects attributable to laudanosine when atracurium is used over long periods. Patients B and C also had lower

CSF concentrations of laudanosine than those seen in dogs, despite greater plasma concentrations (CSF:plasma ratios < 0.1 compared with 0.3–0.6, respectively). This further supports the concept of a species difference in distribution of laudanosine in the CNS.

The plasma and CSF concentrations of laudanosine in patient C (8.65 μg ml^{-1} and 440 ng ml^{-1}, respectively) are greater than reported previously, and considerably greater than those in the two other patients. This is most likely a reflection of the greater rate of infusion and total dose of atracurium used (7.92 g). Despite these concentrations, no CNS side effects were seen either during the infusion or immediately after discontinuation, although EEG was not monitored. The slight difference in the CSF:plasma ratios between patients B and C may reflect the difference in the pathology of the underlying head injuries. Patient B was known to have cerebral contusions, and patient C had generalized cerebral oedema.

Laudanosine accumulated in both plasma and CSF during prolonged infusions of atracurium. The rate of increase and the final concentration of laudanosine within the CSF were smaller in man than in dogs. Concern about the use of prolonged infusions of atracurium based on results in dogs may therefore not be justified.

ACKNOWLEDGEMENTS

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MASSIVE HISTAMINE RELEASE IN A PATIENT WITH SYSTEMIC MASTOCYTOSIS

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A. WOLFF, S. R. BLOOM AND M. MORGAN

SUMMARY

We have measured plasma histamine concentrations, systemic vascular resistance, cardiac output and arterial pressure during laparotomy in a patient with systemic mastocytosis. The patient developed vasodilatation and hypotension during surgery, associated with a massive increase in plasma histamine concentration.

KEY WORDS
Complications: mastocytosis. Histamine: plasma concentration.

The mastocytoses are a group of disorders in which an abnormal proliferation of mast cells occurs. The cutaneous manifestation, urticaria pigmentosa, is the commonest form and was described first in 1869 [1]. Systemic mastocytosis occurs in approximately 10% of all cases, with proliferation of mast cells in other tissues such as bone, liver and spleen. Degranulation of mast cells with release of histamine may occur spontaneously or be triggered by a variety of stimuli which include stress, exercise, alcohol and drugs known to release histamine [2]. Profound vasodilatation following histamine release may result in life threatening hypotension. Bronchospasm does not occur usually [3]. Cases of patients with systemic mastocytosis undergoing surgery have been reported previously [4, 5] and the perioperative management has been reviewed comprehensively [6]. We report a case of systemic mastocytosis in which profound vasodilatation and hypotension associated with a massive increase in plasma histamine concentrations occurred during laparotomy.

CASE REPORT

The patient was a 57-yr-old Portugese man admitted for investigation of syncopal and flushing attacks which were related to meals. One of these attacks had resulted in his admission to hospital cyanosed and hypotensive, but he recovered fully after receiving a short period of ventilation of the lungs and i.v. fluids. He was investigated extensively, but no cause was found for these attacks. Twenty-four-hour ECG Holter monitoring, EEG, conventional radiology including barium swallow and CT scanning of the brain and thorax were normal. Phaeochromocytoma and carcinoid syndrome were considered unlikely on the basis of normal 24-h urinary estimations of vanilmandelic acid and 5-hydroxyindole acetic acid (5HIAA).

Following upper gastrointestinal endoscopy, the patient suffered an acute cardiovascular collapse with profound hypotension and marked flushing of the skin which was treated successfully with i.v. infusion of colloid solutions. He required tracheal intubation and ventilatory support in intensive care for several hours.

Abdominal CT scanning showed an intrahepatic lesion suggestive of an angioma, and a bulky tail of pancreas. It was decided to perform laparotomy to exclude a discrete upper abdominal neuroendocrine tumour which might be secreting vasoactive compounds such as histamine and

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vasoactive intestinal peptide (VIP). Following the laparotomy, which excluded a discrete tumour, a diagnosis of systemic mastocytosis was made. A skin biopsy showed changes consistent with adult onset urticaria pigmentosa and extracutaneous proliferation of mast cells was shown in the spleen removed at laparotomy and in a bone marrow trephine specimen.

The patient was premedicated with oral diazepam 10 mg, ranitidine 150 mg and chlorpheniramine 8 mg 60 min before arrival in the anaesthetic room. A 13-gauge i.v. cannula and a 20-gauge radial artery cannula were inserted under local anaesthesia. Continuous monitoring of arterial pressure and ECG was commenced. Before induction of anaesthesia, somatostatin analogue (Octreotide) 500 µg and hydrocortisone 200 mg were given i.v. Anaesthesia was induced with etomidate 22 mg. Vecuronium 8 mg was given to facilitate intubation of the trachea, and the lungs ventilated with nitrous oxide and enflurane in oxygen.

Continuous monitoring was commenced of oxygen saturation by pulse oximeter and of end-tidal carbon dioxide concentration by capnography. A second peripheral i.v. cannula was inserted, and a thermodilution pulmonary artery catheter and two single-lumen, 16-gauge cannulae were inserted through the right internal jugular vein. The patient was turned to the left lateral position and an extradural catheter inserted at the T5–6 interspace. A bolus dose of fentanyl 100 µg followed by an infusion of fentanyl 1 µg kg^{-1} h^{-1} was given through the extradural catheter. The patient was placed on a warming mattress and all i.v. fluids were warmed. A nasopharyngeal temperature probe and a urinary catheter were inserted. A nerve stimulator was placed over the left ulnar nerve and an infusion of vecuronium given according to the train-of-four response.

Blood samples were taken frequently for subsequent analysis of histamine and vasoactive peptides. Plasma histamine was measured by the double isotope technique described by Brown and colleagues [7]. Under basal conditions plasma histamine concentration is usually less than 0.4 ng ml^{-1}.

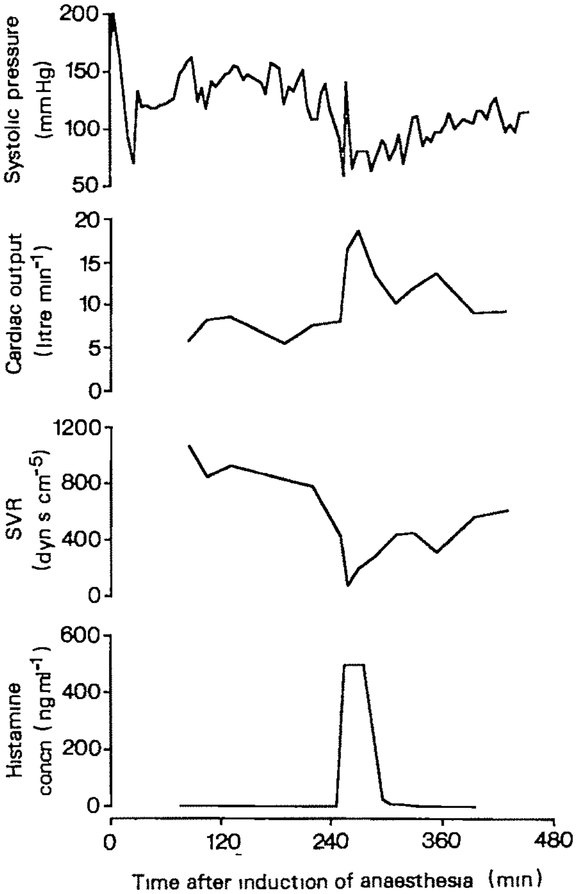

FIG. 1. Plasma histamine concentrations and cardiovascular measurements during laparotomy.

Laparotomy was performed and was normal except for a haemangioma on the surface of the liver and a small aneurysm of the hepatic artery. With the exception of a decrease in systolic pressure to 71 mm Hg 20 min after induction of anaesthesia, cardiovascular variables were stable during the first 4 h. During a needle biopsy of the tail of the pancreas 255 min after induction of anaesthesia, the patient became flushed and hypotensive, with a systolic arterial pressure of 60 mm Hg. Colloid solution was infused rapidly and a bolus of angiotensin (Hypertensin, Ciba) given, followed by an infusion of angiotensin to a total dose of 2 mg. Somatostatin analogue 500 µg was given i.v. At this time, cardiac output was 16.4 litre min^{-1} and systemic vascular resistance 78 dyn s cm^{-5}. Systolic arterial pressure increased to approximately 70–80 mm Hg and this was maintained over a period of 60 min. The patient was completely anuric for 1 h and an infusion of dopamine 5 µg kg^{-1} min^{-1} was started. A subsequent decrease in systolic arterial pressure to 69 mm Hg associated with volume loss responded to transfusion of fluids and i.v. adrenaline 50 µg and then remained at 100–120 mm Hg for the remainder of the operation. The inspired oxygen concentration was increased from 0.35 to 0.5 during the hypotensive crisis as oxygen saturation decreased to 93 %. Auscultation of the chest revealed mild bronchospasm, but there was no difficulty in ventilating the lungs.

A distal pancreatectomy and splenectomy were performed. Following this there was extensive bleeding from cut surfaces. Coagulation studies revealed a prolonged activated partial thromboplastin time of more than 150 s (control range 21–37 s) consistent with heparin release from mast cells. Total blood loss during the operation exceeded 6 litre and the patient was transfused with approximately 7 litre of colloidal solutions including blood and fresh frozen plasma. After operation the patient was transferred to the intensive care unit and the trachea was extubated after 3 h. He made an uneventful recovery and was discharged home after 14 days on high dose oral salicylic acid, ranitidine and astemizole.

Plasma histamine concentrations and haemodynamic data recorded during operation are shown in figure 1. The maximum plasma histamine concentration is shown as 500 ng ml^{-1}, as this was the upper limit of the assay.

DISCUSSION

Intraoperative cardiovascular collapse associated with massive increase in plasma histamine concentrations in a patient with systemic mastocytosis has not been described previously.

The pathological involvement of histamine in human hypersensitivity reactions, classically by IgE dependent stimulation of tissue mast cells, is well established. Human mast cells represent a heterogeneous population and this is reflected in their diverse tissue locations—skin, upper and lower respiratory tract and in gastrointestinal and reproductive mucosa. In this patient, plasma histamine concentrations were monitored over a considerable period of time, during which profound haemodynamic changes occurred. It is likely that other mediators were responsible also for these changes. However, the profound vasodilatation and hypotension coincident with flushing and evidence of coagulopathy suggest considerable mast cell degranulation with release of histamine playing a principal role in the subsequent pathological events. The large sustained increase in plasma histamine concentrations to more than 500 ng ml^{-1} suggests widespread mast cell degranulation rather than a localized response.

There is frequently a delay in making the diagnosis of systemic mastocytosis. Webb, Li and Yam reported a series of 26 patients in whom the mean duration of symptoms and signs was nearly 2 yr before diagnosis of systemic mast cell disease was made [8]. In this patient, a firm diagnosis of systemic mastocytosis had not been made before operation. It was considered that he might have a neuroendocrine tumour such as carcinoid and this influenced our pre- and perioperative management. Demonstration of serotonin production as manifested by increased urinary 5HIAA concentrations remains the mainstay of laboratory diagnosis in carcinoid syndrome, although more than 20 humoral messengers are recognized. A subset of patients with carcinoid syndrome excrete histamine at increased concentrations in their urine and many of these patients have tumours of gastric origin [9].

Preoperative management of patients with mastocytosis is aimed at reducing the risk of mast cell degranulation. This releases histamine, involving both H_1 and H_2 histamine receptors [10] and therefore both H_1 and H_2 receptor antagonists were given. Peripheral block of histamine receptors is inadequate to prevent severe hypotension, and Roberts and colleagues [11] have shown that prostaglandin PGD2 is an important mediator in the hypotensive episodes associated with mastocytosis. High dose acetylsalicylic acid inhibits prostaglandin synthetase and is effective in controlling episodes of vasodilatation. However, in approximately 5 % of patients severe hypotension may be precipitated by aspirin. We did not use aspirin in this patient because the diagnosis had not been confirmed and its effect on bleeding time could have been detrimental. Sodium cromoglycate is poorly absorbed orally and was not shown to improve control of symptoms in patients compared with a combination of H_1 and H_2 receptor blocking drugs in a double-blind crossover trial [12].

Somatostatin analogue has not been evaluated in mastocytosis; it was given to this patient because of its efficacy in the treatment of patients with carcinoid syndrome [13] and in reducing symptoms in patients with VIP tumours [14].

I.v. adrenaline has been shown to be the mainstay of treatment of intraoperative hypotension in patients with systemic mastocytosis [15]. However, catecholamines may aggravate symptoms of carcinoid syndrome, possibly by stimulating tumour hormone release, and should be avoided in carcinoid hypotensive crisis [16]. Angiotensin is a potent pressor agent which acts mainly by a direct action on vascular smooth muscle. It is recommended for use in hypotension induced by carcinoid tumour [16]. It acts mainly on visceral blood vessels; in this patient the use of angiotensin was associated with anuria. As the use of dopamine in the management of the anuria produced no worsening of hypotension, we were confident to use adrenaline in the management of a further episode of hypotension.

Choice of anaesthetic agents for these cases relies on avoidance of agents known to release histamine [6]. Direct measurement of arterial and central venous pressure and insertion of large-gauge i.v. cannulae to allow rapid volume replacement are essential. Potent vasopressor agents should be readily available for use by bolus injection and infusion.

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COMMENTARY

GUEST REVIEWERS FOR 1990

Each manuscript submitted to *British Journal of Anaesthesia* is reviewed by members of the Editorial staff, and also by individuals with particular expertise in the area of study under consideration. All reviewers are asked to consider the scientific merit of each communication and its relevance to the clinical practice of anaesthesia. Consequently, acceptance for publication is based on the views of two or more individuals as to originality, validity and clinical relevance of the information presented.

The Editor would like to acknowledge the significant contributions made by the undernoted individuals who, in addition to the Editorial team, reviewed manuscripts during 1990.

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CORRESPONDENCE

CLINICAL OBSERVATIONS ON ORG 9426

Sir,—I was interested to read the initial clinical report by Dr Wierda and his colleagues on the new intermediate duration steroidal neuromuscular blocking drug, Org 9426 [1].

It would seem unlikely that there were no haemodynamic changes during tracheal intubation and therefore the statement that there were no cardiovascular side effects is inappropriate. Cardiovascular studies on new drugs should be performed during a haemodynamically stable period and preferably with continuous invasive monitoring and recording. Furthermore, if the drug is to be used to facilitate rapid intubation it must be used in a dose larger than 500 $\mu g\ kg^{-1}$. An onset time to maximum block of greater than 3 min (204 s) is considerably slower than that achieved with larger doses of atracurium [2] or vecuronium. I should be interested to see if this low potency drug is still devoid of cardiovascular side effects at greater doses. I suspect its margin of safety for vagolytic or ganglion blocking side effects may not be as impressive as its more potent analogue, vecuronium.

The conclusion that this new compound has the major advantage of offering good to excellent intubating conditions at 1 min (500 $\mu g\ kg^{-1}$) is weak. The mean time (with a wide SD) to 75% block was 68 (30) s, which implies that at 1 min the percentage block at intubation was somewhat less than this. My conclusion would be that the authors' good intubating conditions were created mostly by thiopentone, nitrous oxide, and fentanyl up to 5 $\mu g\ kg^{-1}$. What was the mean (and SD) percentage block of T1 at intubation? What would the intubating conditions be after thiopentone and Org 9426 only? Ideal intubating conditions are provided at 95% block [3].

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Sir,—Thank you for the opportunity to respond to Dr Scott's remarks on our study [1]. His comments concern mainly the cardiovascular aspects and the intubating conditions observed following administration of the drug. The aims of our study apparently have remained unnoticed. As indicated, we investigated the neuromuscular potency, time course of action (250 and 500 $\mu g\ kg^{-1}$) and the intubating conditions (500 $\mu g\ kg^{-1}$) of Org 9426. The cardiovascular variables, in common with other vital signs, were monitored as a routine part of the anaesthetic procedure. As this is a new drug which has been used, we should also look for and report absence or presence of drug-related effects other than that of neuromuscular block.

The lag time and the onset to 75% twitch height depression were significantly shorter following equipotent doses of Org 9426 and vecuronium. The 1-min intubating conditions appeared invariably good to excellent, which is of considerably greater clinical relevance than the percentage twitch height depression of the adductor pollicis muscle at the time of intubation. Dr Scott's statement regarding the degree of block (95%) necessary for ideal intubating conditions is based on papers cited by Ali and Savarese in 1976 [2], which were published between 1966 and 1971. New developments and different views on this issue [3, 4] in the past 25 years have not been mentioned. Dr Scott questions the quality of intubating conditions which we observed, without providing experimental evidence for his statements. Further assumptions are made of possible cardiovascular side effects after larger doses of Org 9426, again without any evidence.

The speculative nature of Dr Scott's comments, illustrated by his conclusion that good intubating conditions were produced mainly by the anaesthetic technique, ignores the degree of redistribution of thiopentone between the time of induction and the end of stabilization of the twitch before administration of Org 9426 (usually about 5 min) and experimental evidence to the contrary [5].

J. M. K. H. WIERDA
S. AGOSTON
Groningen

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MANAGEMENT OF MAJOR TRAUMA

Sir,—We wish to comment on some points raised by Dr Clark's editorial "Improving the management of major trauma" [1]. We agree that there should be a greater medical involvement in the training of ambulance personnel in the U.K. However, recently there has been a suggestion that ambulance officers should assess the competence of general practitioners to perform cardiopulmonary resuscitation in the M.R.C.G.P. examination [2]—a suggestion we find totally unacceptable. We recommend that doctors involved in the pre-hospital environment should be encouraged to achieve the Diploma in Immediate Care (DIP. I.M.C. R.C.S. ED.) (further information available from: Royal College of Surgeons of Edinburgh, 8 Nicholson Street, Edinburgh).

Centralization of trauma centres will not necessarily stop the arrival of the seriously injured at the District General Hospital casualty departments. Hence it is important that algorithms as laid down by Advanced Trauma Life Support (ATLS) should be used more widely in these units [3]. We suggest that the "designated team leader" could also be an anaesthetist; trauma is not solely a surgical problem and up to 90% of traumatized patients do not initially require a surgeon [4] As hypoxia "wrecks the machinery", the anaesthetist is in the ideal position to optimize tissue oxygen delivery. The management of the severely injured involves resuscitation, anaesthesia and life support procedures, often simultaneously.

However, anaesthesia for trauma is not anaesthesia for the patient with a full stomach; and thus there is a need for a subspecialty—the trauma anaesthetist. This proposal would be based on the trauma anaesthesia/critical care specialists (TA/CCS) as used at the Maryland Institute of Emergency Medical Systems in the U.S.A. [4]. The TA/CCS is the first member of the trauma team to take charge of the injured patient arriving at the Shock Trauma Centre. In Europe, the trauma patient is directed at all stages by the anaesthetist or reanimatologist [5, 6].

We agree that the role of helicopters in accident services in the U.K. merits further research and evaluation. Recently, the advantages of helicopters in transfers between hospitals were published, but without mention of the disadvantages [7]. Nobody doubts that helicopters may improve survival significantly in civilian truma [7], but they are expensive and crashes do occur, sometimes with fatal outcome. The criteria for selecting patients who will benefit from helicopter transfer, and guidelines for operational conditions by the aviation authorities need to be established [8]. There are also potential problems of interference between aircraft electronics and electrical medical equipment that require consideraton [9].

W. F. deMello
J. Restall
Aldershot

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Sir,—Thank you for the opportunity to respond to the comments of Drs deMello and Restall. As they indicate, centralization of the management of seriously injured patients in Trauma Centres will not exclude completely their admission to Accident and Emergency (A & E) departments. However, many of the recommendations in the Royal College of Surgeons report [1], such as improved training of ambulance personnel in the assessment of the severity of injury with better radiocommunication to, and medical input from the Trauma Centre should ensure that most patients are conveyed to the appropriate hospital. Training of all A & E senior registrars within Trauma Centres, good local liaison between the Trauma Centres and referring A & E departments with specialized interhospital transfer have been recommended and should improve the care of any seriously injured patient admitted to an A & E department. The Royal College of Surgeons of England has now established Advanced Trauma Life Support courses in the United Kingdom and, hopefully, the algorithmic approach taught by these courses will become more widely used, resulting in a more unified approach to the injured patient.

As the report recommends, the anaesthetists working in the Trauma Centres will be specially trained in trauma management. While I agree that the trauma anaesthetist will have a central role, being with the patient from admission to the Trauma Centre until their admission to the Intensive Care Unit, no single specialty has a monopoly on the qualities which would make a good team leader.

Helicopters are expensive and have limitations. Their use can be justified only to reduce the time between injury and appropriate care for the seriously injured patient [2]. It requires proper evaluation to find their cost-effective role within an integrated trauma system in the United Kingdom.

C. Clark
Edinburgh

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HALOTHANE HEPATITIS

Sir, — Dr Speedy, in his paper "Halothane Hepatitis: A Case Report" [1], speculates on the possibility of repeated halothane-induced hepatic failure in a patient who received 12 anaesthetics over a 24-yr period. Seven of the anaesthetics probably included halothane.

It is not surprising to find that concentrations of the non-specific tissue enzyme AST(SGOT) were increased after surgery for a burst abdomen, total hip replacement, revision total hip replacement and a septic foot. Much is attributed to the anaesthetic agent used and little is said about the patient's drug history, alcohol intake, contact with hepatitis carriers, blood transfusions, intra- and postoperative hypotension, hypercapnia, hypoxia and septicaemia. On two occasions the author speculates that halothane would probably have been used, although it was not recorded on the anaesthetic record! He then goes on to make assertions based on this speculative information.

The patient experienced unexplained hepatitis following halothane, but was exposed subsequently to halothane several more times. If there is a message in the report it is that anaesthetists should read the patient's old notes! The case report is presented as evidence in favour of the advice on using halothane, issued by the Committee on Safety of Medicines. The Committee may be right (I happen to think they are wrong), but this case report is so short of reliable information that it would be wishful thinking to present it as evidence substantiating the Committee's view.

H. WARK
Sydney, Australia

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Sir, — Thank you for allowing me to reply to Dr Wark's letter of criticism regarding this case report.

Dr Wark's main criticism of this paper appears to be that it is "short of reliable information" and "speculative" in nature. Concerning the reliability of information, it must be realized that this case history spans some 25 yr. In the past, records may not have been so comprehensive or well informed as legal prudence requires today. Traditional methods of case note record keeping in this country are open to loss of information in a sea of more trivial detail. I agree with the sentiments on the importance of reading the patient's old notes before embarking on anaesthetic care. I am sure, however, the anaesthetists involved found the task of sifting through what was in this case a large tome of disordered clinical information, a difficult and daunting task. Admission notes in every case save one made no mention of hepatitis, and there was no attempt to place such important information in a prominent place (e.g. front of case note folder, current drug charts).

On the criticism of speculation: on the two occasions where the use of halothane was not clearly documented, there is circumstantial evidence that halothane may have been used. I stress this fact in the appropriate place in the case report. If Dr Wark is suggesting that we should disregard all circumstantial evidence as speculative and therefore unworthy of serious consideration, then perhaps we should also stop trying to persuade patients to give up smoking and impose sensible limits on their cholesterol, salt and alcohol intake!

Dr Wark states that increased liver enzyme concentrations following surgery are to be expected. I am not sure why he thinks these were increased after the patient burst his abdomen, because there are no results from this period; indeed, the assay was not available from the chemical pathology service at that time. Minor increases in concentrations of liver enzymes are associated commonly with any physiological stress, but rarely, in my experience, does one see an increase greater than twice normal after routine uncomplicated surgery. In this patient's case the transaminase concentrations were more than five to 10 times normal on several occasions. Also, on several occasions the bilirubin concentration was grossly increased and the patient clinically jaundiced.

Dr Wark suggested that the patient's hepatic dysfunction might have been attributable to several other causes. This, of course, has been the main reason for the years of debate on whether or not halothane hepatotoxicity is a real entity, and traditionally, the diagnosis is arrived at by exclusion. In several instances preoperative liver function testing showed that there was no liver dysfunction before surgery and anaesthesia. On the occasion of the most severe illness following halothane, the physicians at Kings College Hospital Liver Unit ruled out other drugs as a cause for the hepatotoxicity, and repeated testing for viral antigens was negative. Blood transfusions may cause mild increase in bilirubin concentrations, but not dysfunction of this degree; again, major transfusion reaction was ruled out as a cause after careful checking of crossmatching. Similarly, there was no evidence of severe septicaemia. Perhaps another piece of circumstancial evidence is worth repeating: on none of the five occasions when halothane was definitely *not* used was there any evidence of liver dysfunction.

H. SPEEDY
Leeds

A SECOND TIME-STUDY OF THE ANAESTHETIST'S INTRAOPERATIVE PERIOD

Sir, — Once again [1] we are encouraged to use computerized systems for generating anaesthetic records. Once again I draw attention to the possible pitfalls.

In their reply to an earlier letter [2], Drs McDonald and Dzwonczyk [3] pointed out correctly that trials to assess the effect of computerized records on the safety of anaesthetic practice may not be feasible, but that does not absolve them from considering the implications of their suggestion. No matter how inexpensive computerized records may become, they will always be more expensive than hand-written charts: we must have some idea of their real benefit before suggesting their use in everyday practice.

McDonald and co-authors regard filling in the chart as a "repetitive clerical task" [3] that takes anaesthetists' attention away from direct observation of the patient for 10–12% of the intraoperative period [1]. An equally testable hypothesis is that filling in the chart helps to keep anaesthetists in touch with their patients. There are other questions: Is there any evidence that anaesthetists fail to notice critical events because they are filling in a chart? Do anaesthetists spend so long at this task at any one time that an unnoticed critical event could progress to harm the patient? How do we avoid incorrect interpretations — perhaps by non-medical people — of erroneous information recorded automatically on a computerized chart?

Manufacturers are only too willing to persuade us that their sophisticated and expensive equipment is essential to the safety of our patients. We cannot just play hunches and make assumptions; we must make well-balanced decisions before spending public money.

N. W. GOODMAN
Bristol

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Sir, — I was interested to read the paper of McDonald and colleagues on a time-study of the anaesthetist's intraoperative period [1], particularly the method of monitoring the anaesthetist and the resultant division of time. Anaesthetists were monitored by video camera, having been informed that they were the subjects of the study. Results showed that 70% of the time was spent monitoring the patient and record keeping, and that no other activity took up more than 10%.

Whilst these results are commendable, I wonder how much they reflect the true situation. I feel that any anaesthetist informed that he was to be filmed during a case would be acutely aware that his every move was being recorded and analysed; is it any surprise, therefore, that the majority of time spent was in monitoring the patient, with negligible time spent talking or idling? I feel the true situation may be somewhat different, and only would be revealed by surveillance of anaesthetists blissfully unaware of an all-seeing video camera.

D. SUTTON
Southampton

REFERENCE

1. McDonald JS, Dzwonczyk R, Gupta B, Dahl M. A second time-study of the anaesthetist's intraoperative period. *British Journal of Anaesthesia* 1990; 64: 582–585.

Sir, — Thank you for the opportunity to reply to the letters of Dr Goodman and Dr Sutton.

While it may be true that computerized intraoperative records "will always be more expensive than hand-written charts", the cost: benefit ratio may improve to a point at which everyday use of these machines will be both practical and realistic, even in view of the financial limits of the health service. The cost of this technology, in common with other computer technologies, is likely to come down in the future, so that automatic record keeping will be an attractive alternative to the manual method.

The advantages and disadvantages of automatic patient record keepers that affect the benefit side of the cost: benefit ratio have already been discussed [1, 2]. Dr Goodman has voiced the primary potential disadvantage of automatic record keepers. These devices may take the anaesthetist out of touch with the patient [2]. However, presently there is no convincing evidence to support this contention.

Dr Goodman's point concerning erroneous information is one which must be considered from both sides of the record keeping discussion. It is true that the automatic record keeper will record artefactual data that are not processed out by the monitors, but the manual record keeper — that is, the anaesthetist — also may record artefactual data. For example, during a clinically demanding period when the anaesthetist is attending to the patient, he/she often does not have the opportunity to record patient information for an extended period of time. The anaesthetist must then rely on memory when filling in the chart. There are examples in the literature of actual and manually recorded data under these circumstances which were substantially different [1].

An important advantage of automatic record keepers is that they produce an objective, legible, complete and accurate data sheet. Such a record is more supportive of a clinician than handwritten records in medico-legal issues [1].

Although we agree with Dr Sutton that a preferable methodology in our study would have been to video tape the anaesthetists while they were "blissfully unaware of an all-seeing video camera", our institution requires us to obtain verbal consent from the anaesthetists to be filmed.

R. DZWONCZYK
J. S. MCDONALD
B. GUPTA
M. DAHL
Columbus, Ohio

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British Journal of Anaesthesia 1990; **65**: 843–845

BOOK REVIEWS

Preparing for the Anesthesia Orals—Board Stiff. By C. J. Gallacher and D. A. Lubarsky. Published by Butterworth, Stoneham Ma. Pp. 200; indexed; illustrated. Price £26.00.

As would be expected from the first part of the title, this book is directed towards candidates preparing for the American Board of Anesthesiology oral examination. As may be anticipated from the second part of the title, it is not in a conventional textbook format.

The two authors, both Assistant Professors in North Carolina, have set out to prepare a short study guide to assist in preparation for oral examinations. They have prepared a series of sample questions covering a wide range of anaesthetic practice. The questions are addressed in a logical manner, with guidance in identifying the key points in a question, and the basis of an answer to each point is given. Although written for an American audience, the sample questions are of a standard similar to those in the Part III F. C. Anaes. oral examinations, —for example management of a patient with a head injury, failed intubation in obstetrics. So much for the good points.

The main problems with this book is that the sensible advice and answers are rather obscured by a flippant humour, which is amusing for the first few pages, but rapidly becomes wearing. From a personal view, it would be like trying to study while being forced to watch reruns of American sit-coms. To sample the style one need only list some chapter titles: "I don't know nuthin' 'bout birthin' no babies, Miz Scarlet", "Pate", and "Sydney Greenstreet plays the fat man" deal with the anaesthetic problems in obstetrics, liver disease and morbid obesity, respectively.

There are some very good points in this book regarding preparation for the conduct of an oral examination, but this style of writing makes it hard work. It may be worth a quick look through for Part III F. C. Anaes. candidates in need of some light relief.

C. S. Reilly

Scientific Foundations of Anaesthesia: The Basis of Intensive Care. Edited by C. Scurr, S. Feldman and N. Soni. Published by Heinemann Medical Books, Oxford. Pp. 745; indexed; illustrated. Price £80.00.

The fourth edition of this book has added Intensive Care to the title and now includes Neil Soni as an editor to give credence to its wider scope. I remember well the first edition, published in 1970, as the Fellowship examination had just changed to include Physics and Clinical Measurement and there were virtually no books on these important areas of anaesthesia. *Scientific Foundations* was one of the key texts of the time and was used extensively by examination candidates. How has it weathered the past 20 years?

The book is now a substantial 700+ pages and has been produced to a high standard by the publishers, Heinemann. It is divided into four sections: Physical basis of the science of anaesthesia, Physiological basis of the science of anaesthesia, Pharmacological basis of the science of anaesthesia and Anaesthetic apparatus and monitoring. The first section, on the physical basis, covers the basics of clinical measurement. The section on the physiological basis is further subdivided into the cardiovascular system, respiration, neuroendocrine systems, metabolic processes, body fluids and special physiology and occupies about 380 pages, compared with only about 150 pages on the pharmacological basis of anaesthesia. This marked bias in favour of physiology makes the book appear a little unbalanced. The editors are to be congratulated on the calibre of the authors of the chapters. It would be invidious to mention individual authors, but many of the major contributors to anaesthetic research are represented in this book. On the whole, they have produced succinct and topical summaries of their particular field of interest

As I know from personal experience, one of the problems of writing short chapters for books of this type is that core knowledge changes little and this tends to lead to some duplication with other publications from the same author. For example, Covino provides an excellent brief review of the pharmacology of local anaesthetic agents in just over 5 pages. However, Covino has also written a longer chapter on the same subject in Nunn, Utting and Burnell Brown. One of the two tables and both figures in *Scientific Foundations* are found in a similar form in the larger textbook. This raises the question of the continuing need for a book such as *Scientific Foundations* when the modern generation of anaesthetic textbooks such as Nimmo and Smith, and Nunn, Utting and Burnell Brown already devote considerable space to scientific aspects.

In general, I consider that *Scientific Foundations* still has a useful role. The Editors emphasize that there have been extensive revisions to the current text and there are some useful innovations. In particular, David Gadian discusses the theory of nuclear magnetic resonance in only 2 pages. It is a pity that the editors were not prepared to consider other important growth areas in modern clinical measurement.

Should a trainee anaesthetist buy this book? I think probably yes, but not at the expense of one of the large textbooks of anaesthesia. However, my reluctance to recommend it unreservedly to junior staff is tempered by the fact that I am referring to my copy with increasing frequency. I suspect that those innovative qualities of the 1970 edition, particularly clinical measurement, will be sufficient to ensure that a fifth edition will be necessary.

G. M. Hall

Raised Intracranial Pressure — A Clinical Guide. By B North and P. Reilly. Published by Heinemann Medical Books, Oxford. Pp. 109; indexed; illustrated. Price £17 50

This book gives a good introduction to the management of increased intracranial pressure. In general, it is written clearly, read easily and well illustrated. The text is organized well and printed clearly, with a comprehensive index. It provides straightforward explanations for several physiological concepts central to the measurement and treatment of increased intracranial pressure and includes some very useful practical advice. There are chapters on anatomy and physiology of the cranial contents, pathology and clinical and radiological features of increased intracranial pressure, indications for, methods of measurement of and interpretation of intracranial pressure recordings, and methods for control of intracranial pressure. The subject is covered very thoroughly and provides useful information for doctors and nurses working in intensive care units associated with neurosurgical units.

Because it is written by neurosurgeons it gives a neurosurgical rather than an anaesthetic perspective of the subject. The section on the effects of anaesthetic agents on intracranial pressure in chapter 3 is basically correct, but very brief, and seems to suggest that volatile anaesthetic agents are not inhalation agents. The reference to etomidate being withdrawn from clinical use is not strictly correct, as it has only been withdrawn for use by continuous infusion.

There are some spelling mistakes and other errors, but in general they do not detract from the clarity of the text. In chapter 2 the explanation of the mechanism of the increase in cerebral blood volume caused by an increase in cerebral blood flow is too simplistic. In table 2 the authors state that neuroleptanalgesia decreases intracranial pressure, whereas most authorities would agree that it has no effect and that the effects may depend on the choice of agents. The description of autoregulation on page 18 is confused by the inclusion of a sentence describing the different cerebral blood flows for grey and white matter. Figure 4.1 has transposed the best motor response and best verbal response on the Glasgow Coma Scale, and abnormal flexion is omitted from the scale throughout, but the authors do explain their reasons for this omission. On page 59 the explanation of pressure volume index would be clearer if opening pressure was defined. On page 59, line 1, arterial pulse should read arterial pressure. The i.v. administration of glycerol is mentioned without reference to the fact that concentrations of 20% or more may cause haemolysis.

This book achieves its aim of being an easily readable practical guide to the detection and management of increased intracranial pressure. However, all the information which is relevant to anaesthetists is contained in the standard textbooks on neurosurgical anaesthesia and intensive care which also contain comprehensive accounts of the effects of anaesthetic agents on cerebral blood flow and intracranial pressure. Therefore, I would not recommend anaesthetists to purchase this book, although it would be useful to have a copy in the libraries of intensive care units and departments of anaesthesia.

E. Moss

Resuscitation Handbook. By P. J. F. Baskett. Published by Gower Medical Publishing, London. Pp. 119; indexed; illustrated. Price £9.95.

For many years the author has been an enthusiastic innovator and teacher of cardiac and trauma life support and this handbook is a distillation of his extensive experience. It is a clear, concise manual in five sections with an up-to-date bibliography. Colour is cleverly used to emphasize points, outline descriptions and improve the quality of the illustrations.

The introductory section, 7 pages, discusses the causes of cardiorespiratory arrest, infective hazards and definitions of death. The second section, 70 pages, is on cardiac life support, starting with Assessment, then Basic Life Support and finally, Advanced Restoration of the Spontaneous Heartbeat. The algorithms reflect the current teaching of the Resuscitation Council (U.K.). The descriptions of the techniques are concise; important messages are emphasized in blue. While the illustrations of manoeuvres are clear and followed easily, some of the diagrams of equipment lack this clarity.

The third section describes priorities in Trauma Life Support, covering the primary survey, resuscitation of vital functions and the secondary survey. In 36 pages, there is a comprehensive review of problems caused by trauma, subdivided into airway, breathing and circulation including descriptions of securing vascular access. The secondary survey systematically examines other areas to include head, chest, abdominal and limb injuries, finishing with burns and cold injury.

The penultimate section, on Pain Relief, is a useful reminder of the importance of this topic, which often has a low priority.

The final table of skills identifies individual or group targets which can only be attained by constant practice.

The problems of children, whether cardiac or trauma resuscitation, are discussed only briefly amid the adult management; this difficult area needs to be covered in greater depth.

This handbook (the size of *British Journal of Anaesthesia*, with a protective plastic cover) provides not only a stimulating introduction for medical students, nurses and paramedics, but also a convenient reference for any doctor involved in Emergency Medicine or Trauma Care — anaesthetist, surgeon or physician. Candidates for postgraduate exams or those enrolling on A.C.L.S. or A.T.L.S. courses will find it a valuable primer. Most libraries will need several copies, but as it is good value for money, a personal copy will pay dividends in improved standards of resuscitative care.

T. O'Carroll

Clinical Applications of Ventilatory Support. Edited by R. J. Kirby, M. J. Banner and J. B. Downs. Published by Churchill Livingstone, New York. Pp. 546; indexed; illustrated.

This large and nicely produced book is a disappointment. I suspect that this is in part because the division between the technical aspects of providing ventilatory support, and the physiology and pathology of the recipient of the support is almost impossible to define. In the U.S.A., however, this division is a professional and fiscal one, and this unhappy separation may have something to do with the fluctuating levels of sophistication of explanation, description and illustration found from chapter to chapter. Consequently, the editors have attempted to span an impossible range of subjects, often in limited depth, in their quest to "get it all in".

This book starts with an entertaining and individualistic chapter by Trier Morch on the history of mechanical ventilation, which is marred only by the lack of linkage between the text and the list of references that follows. There then follows a poor chapter with occasionally incorrect diagrams on the principles and design of ventilators. This chapter in particular would benefit from a more rigorous approach to the basic physics, but the whole book would benefit from examples provided from good laboratory traces of pressure, flow and volume made with a rectilinear recorder, and consistent and correct use of the Pappenheimer terminology for respiratory physiology. In fact, this might reduce the errors such as $P_l = P_{aw} - P_{pl}$, $C_{LT} = V/(\text{PIP} - \text{PEEP})$, and $C_{dyn} = \Delta V / \Delta P$ (peak).

There are chapters on modes of support, weaning, monitoring and complications, the inevitable medico–legal chapter, and a final chapter on safety which is illustrated almost exclusively from a single source. There is considerable overlap, such that one well-known diagram, based on observations in two subjects, is presented in two different forms on three occasions, with on each occasion an authoritative statement that was no more than a postulate in the original work.

Unless the reader is already familiar with the principles of respiratory physiology, this book will act as a source of much confusion rather than clarity. Given a knowledge of the principles, the mistakes and errors can be winnowed out, and some of the chapters on the clinical aspects of artificial ventilation are satisfactory, but I would not recommend this book for serious use, apart from the fascinating historical chapter.

G. B. Drummond

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